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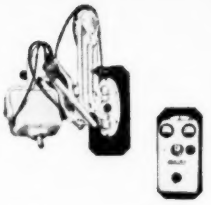

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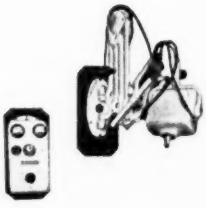

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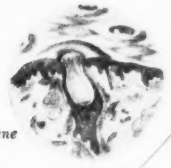

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1. Bednar, G. A.: South. M. J. 46:298 (March) 1953.
2. Wright, C. S., et al.: A. M. A. Arch. Dermat. & Syph. 67:125 (Feb.) 1953.
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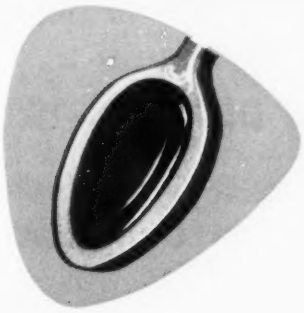

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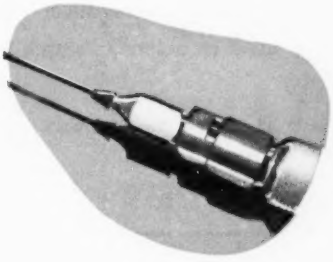

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*Sulzberger, M. B., and Wolf, J.: Dermatology, Essentials of Diagnosis and Treatment, Chicago, Year Book Publishers, Inc., 1952, p. 323.

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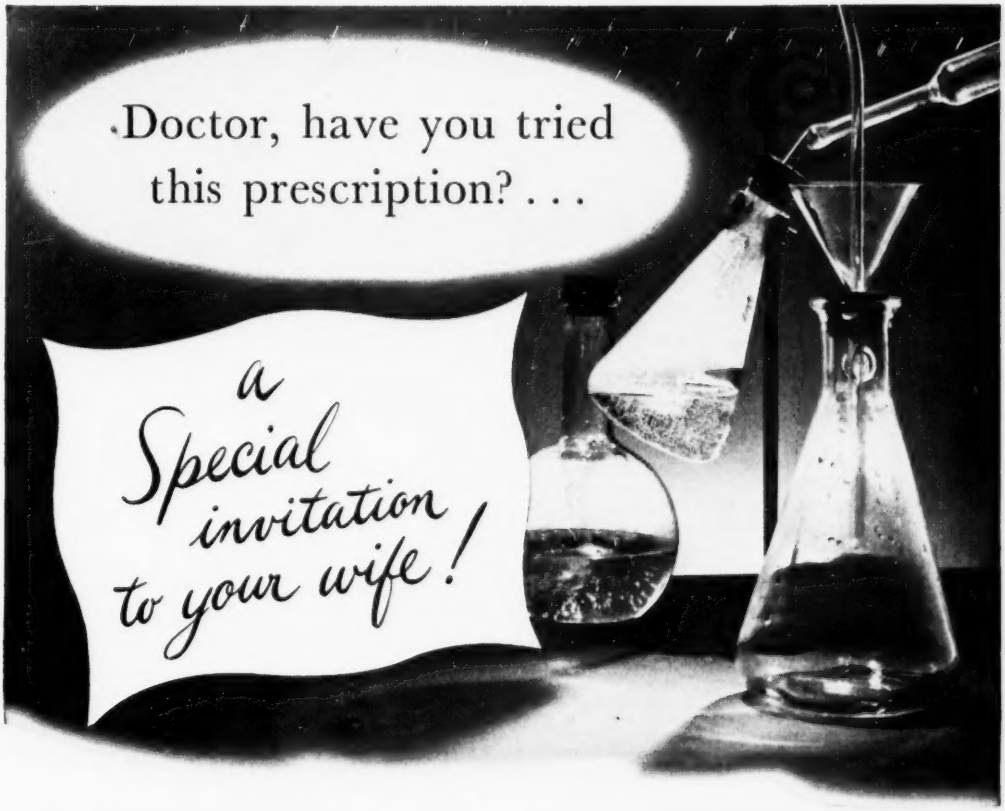

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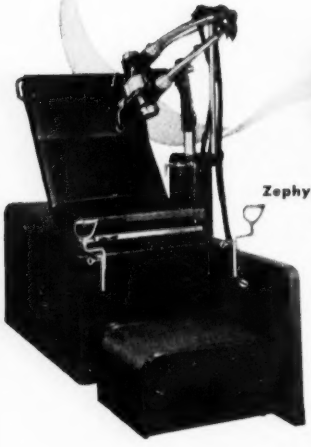

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Archives of Dermatology and Syphilology

VOLUME 68 AUGUST 1953 NUMBER 2

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COMPLEMENT IN DISSEMINATED (SYSTEMIC) LUPUS ERYTHEMATOSUS

JOSEPH A. ELLIOTT Jr., M.D.
AND
DON R. MATHIESON, M.D.
ROCHESTER, MINN.

DISSEMINATED (systemic) lupus erythematosus is a relatively rare disorder. Little is known about its cause, but, because it has features in common with serum sickness, it has been postulated that the disease may be a manifestation of an antigen-antibody reaction.[1] Other workers disagree with this concept.

Heidelberger [2] has stated that complement acts as an "intensifier" of immune mechanisms. One of us (Mathieson) observed that serum from patients who had disseminated lupus erythematosus produced less hemolysis of sheep erythrocytes than did serum from normal persons. In nine patients who had lupus erythematosus, Sipos and Jáksó [3] found normal values for complement in five, slight decrease in value in three, and pronounced decrease in one. In view of these observations, it was considered that an accurate determination of the amount of complement in serum by the quantitative methods developed by Mayer and associates [4] and by Kent and co-workers [5] was warranted for patients who had disseminated lupus erythematosus.

Fellow in Dermatology and Syphilology, Mayo Foundation (Dr. Elliott Jr.), now practicing in Charlotte, N. C.; Section of Clinical Pathology, Mayo Clinic (Dr. Mathieson).

Abridgment of thesis submitted by Dr. Elliott to the Faculty of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

1. (*a*) Fox, R. A.: Disseminated Lupus Erythematosus—an Allergic Disease?, Arch. Path. **36**:311-315 (Sept.) 1943. (*b*) Rich, A. R.: The Role of Hypersensitivity in the Pathogenesis of Rheumatic Fever and Periarteritis Nodosa, Proc. Inst. Med. Chicago **15**:270-280 (March 15) 1945. (*c*) Teilum, G.: Pathogenetic Studies on Lupus Erythematosus Disseminatus and Related Diseases, Acta med. scandinav. **123**:126-142, 1946. (*d*) Welsh, A. L.: Specificity of Streptococci Isolated from Patients with Skin Diseases: Studies on Pemphigus, Dermatitis Herpetiformis, Lupus Erythematosus and Erythema Multiforme; Lupus Erythematosus Disseminatus, J. Invest. Dermat. **10**:305-325 (May) 1948.

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3. Sipos, K., and Jáksó, G.: Bestimmungen des Komplementgehaltes im Blutserum Hautkranker, Dermatologica **98**:104-112, 1949.

4. Mayer, M. M.; Eaton, B. B., and Heidelberger, M.: Spectrophotometric Standardization of Complement for Fixation Tests, J. Immunol. **53**:31-35 (May) 1946.

5. Kent, J. F.; Bukantz, S. C., and Rein, C. R.: Studies in Complement Fixation: Spectrophotometric Titration of Complement; Construction of Graphs for Direct Determination of the 50 Per Cent Hemolytic Unit, J. Immunol. **53**:37-50 (May) 1946.

MATERIALS AND METHODS

The amount of complement was determined in serums from 27 patients in whom the diagnosis of disseminated lupus erythematosus was established at the Mayo Clinic. The content of complement was determined on the basis of the ability of the serum to cause hemolysis of sheep erythrocytes. The diagnosis was based on the past history or present findings of polyserositis, malaise, recurrent fever, and cutaneous lesions, together with results of laboratory tests that usually are accepted as characteristic of disseminated lupus erythematosus. Serums from 60 unselected blood donors served as controls.

Suspension of Sheep Erythrocytes.—Blood was drawn aseptically from sheep into an equal volume of modified Alsever's solution[6] and stored in a refrigerator at 3 to 6 C. Erythrocytes stored in this medium became constant in their susceptibility to lysis by complement and antibody after four days and remained at the same level of susceptibility for at least 10 weeks.[7]

The required volume of preserved blood was removed aseptically each day that tests were performed and washed three times by centrifugation with barbital-sodium chloride buffer.[8] After the third 10-minute centrifugation at 2,000 rpm, the volume of packed erythrocytes was noted and an approximately 2% suspension was prepared by dilution with barbital-sodium chloride buffer.

This suspension was standardized spectrophotometrically as follows: Four-tenths milliliter was lysed by mixture with 1.6 ml. of distilled water; the mixture was centrifuged for five minutes at 2,000 rpm with the tube stoppered. The supernatant fluid was decanted into a cuvette measuring 10 by 75 mm., and the optical density of this fluid was determined at 555 mμ (the wave length at which oxyhemoglobin has a minimal transmittance) against distilled water as a reference in a Model 6A Coleman Junior spectrophotometer. The mean optical density of the hemolyzed sample was adjusted to 0.500 ± 0.01 by the addition or removal of the barbital-sodium chloride solution. The final volume (V_2) of suspension that was required to produce this optical density was determined according to the formula $V_2 = \frac{V_1 OD_1}{0.500}$, in which V_1 is the volume of suspension that produces the observed optical density OD_1.

Sensitization of Erythrocytes.[8b]—The adjusted suspension of erythrocytes was sensitized by the addition of an equal volume of the proper dilution of hemolysin.[9] This dilution was determined by titration (Table 1) of each new package of hemolysin and was checked every three months during the study. Components were added in the order given; the total volume in each tube was 0.8 ml. The tubes were incubated for 30 minutes at 37 C. The greatest dilution of hemolysin that produced complete lysis was taken as one unit. Four units were used for sensitization; for example, if the greatest dilution that gave complete lysis was 1:12,800, then

6. This contains 2.05 gm. of dextrose, 0.8 gm. of sodium citrate, 0.42 gm. of sodium chloride and 0.055 gm. of citric acid per 100 ml. of distilled water. The solution is sterilized by passage through a sintered glass filter of bacteriologic type.

7. Bukantz, S. C.; Rein, C. R., and Kent, J. F.: Studies in Complement Fixation: Preservation of Sheep's Blood in Citrate Dextrose Mixtures (Modified Alsever's Solution) for Use in the Complement Fixation Reaction, J. Lab. & Clin. Med. **31**:394-399 (April) 1946.

8. (*a*) This buffer solution was prepared by dissolving 5.75 gm. of 5,5-diethyl barbituric acid in 500 ml. of hot water and then adding 85 gm. of sodium chloride and 3.75 gm. of sodium 5, 5-diethyl barbiturate. After the solution cooled it was made up to 2,000 ml. with water. One gram of magnesium chloride (0.0005 molar $MgCl_2.6H_2O$) and 0.22 gm. of calcium chloride (0.00015 molar $CaCl_2.2H_2O$) were then added. Each day, one part of this stock solution was diluted to five parts with water. (*b*) Kabat, E. A., and Mayer, M. M.: Experimental Immunochemistry, Springfield, Ill., Charles C Thomas, Publisher, 1948, Chap. 4, pp. 97-139. (*c*) Mayer, M. M.; Osler, A. G.; Bier, O. G., and Heidelberger, M.: The Activating Effect of Magnesium and Other Cations on the Hemolytic Function of Complement, J. Exper. Med. **84**:535-548 (Dec.) 1946.

9. Rabbit antisheep hemolysin was obtained as a 50% solution in glycerin (Sharp and Dohme). A 1:100 stock dilution containing 2 ml. of 50% glycerinized hemolysin, 94 ml. of barbital-sodium chloride buffer and 4 ml. of 5% phenol in water was prepared and kept in the refrigerator.

a 1:3,200 dilution of hemolysin was mixed with an equal volume of the suspension of sheep erythrocytes.

The diluted hemolysin was mixed and poured slowly into the suspension of erythrocytes with constant agitation; the mixture was incubated at 37 C. for 10 minutes and kept in ice water thereafter. This reagent was prepared each day.

Serum Complement.—Blood was obtained from each patient by venipuncture and was transferred to a centrifuge tube. The sample was kept at room temperature for 20 minutes and then centrifuged for 20 minutes at 2,000 rpm.

Titration of Complement.—The preliminary titration of complement by the 100% method was carried out by means of eight tubes, each of which contained 1 ml. of twofold serial dilutions of the patient's serum in barbital-sodium chloride buffer, starting with a 1:2 dilution; 0.2 ml. of

TABLE 1.—*Titration of Hemolysin*

Material	Quantities in Each Tube, Ml.				
	1	2	3	4	5
Barbital-NaCl buffer	0.20	0.20	0.20	0.20	0.20
Hemolysin (1:100)	0.20	Buffer and hemolysin are mixed in tube 1; 0.2 ml. is transferred to tube 2 and mixed. These twofold dilutions are continued, and, finally, 0.2 ml. is discarded from tube 5.			
Unsensitized 2% suspension of sheep erythrocytes	0.20	0.20	0.20	0.20	0.20
Complement (1:20) *	0.20	0.20	0.20	0.20	0.20
Barbital-NaCl buffer	0.20	0.20	0.20	0.20	0.20
Final dilution of hemolysin	1:1,600	1:3,200	1:6,400	1:12,800	1:25,600

* The contents of a 7 ml. vial of lyophilized guinea pig serum (Sharp and Dohme) were restored to 5 ml. with the supplied stabilizing diluent. One part of this solution was diluted to 20 parts with barbital-sodium chloride buffer.

TABLE 2.—*Titration of Complement*

Material	Quantities in Each Tube, Ml.						
					100% Hemolysis		Blank
	1	2	3	4	5	6	7
Sensitized 1% suspension of sheep erythrocytes	0.80	0.80	0.80	0.80	0.80	0.80	0.80
$MgSO_4$ (10%)	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Barbital-NaCl buffer	0.89	0.84	0.79	0.74	0.19	0.19	1.19
Serum, proper dilution	0.30	0.35	0.40	0.45	1.00	1.00	....

the sensitized suspension of sheep erythrocytes was added to each tube. The tubes were incubated for 30 minutes at 37 C. The greatest dilution of serum that produced 100% hemolysis (C'_{H100}) was determined after the tubes were centrifuged at 2,000 rpm for five minutes. Normal serum showed complete hemolysis at a dilution of 1:128.

Calculation of the amount of serum necessary to produce 50% hemolysis (C'_{H50}) was based on the dilution of serum that produced 100% hemolysis in preliminary tests. For example, if C'_{H100} was 1:128, a dilution of serum of 1:50 was used to determine the C'_{H50}; if C'_{H100} was 1:32, a dilution of 1:12.5 was used.

The final titration of complement was carried out as shown in Table 2. Seven tubes were set up in a cold-water bath. The solutions were added in the order given in Table 2 and shaken to insure complete mixing. The tubes were stoppered to prevent evaporation and were then incubated for 45 minutes at 37 C.; they were immersed almost completely and shaken thoroughly every 10 minutes. The tubes were then centrifuged for 10 minutes at 2,000 rpm, and the supernatant fluid from each was decanted into a cuvette measuring 10 by 75 mm.; the optical density of the fluid was determined at 555 mμ by comparison of it with the supernatant fluid from the

blank tube. The amount of hemolysis expressed as per cent was calculated by division of the observed optical density by the average optical density of the mixtures that disclosed 100% hemolysis. C'_{H50} was determined by plotting the per cent hemolysis (Y) against the logarithm of the milliliters of serum (X) on graph paper with logistic ruling,[10] which corresponds to the Von Krogh equation for hemolysis. One-half the volume of serum actually used in the titration was used in the calculation in order to determine C'_{H50} on the basis of a volume of 1 ml., since the total volume in each tube in the titration was 2 ml.[11]

RESULTS

The C'_{H50} for the serums of 50 normal blood donors ranged from 0.00268 ml. to 0.00480 ml., with a mean value of 0.003745 ml. and a standard deviation of 0.000456 ml. The coefficient of variation was 12.2% and the mean slope (1/n) when Y was plotted against log X on "logit" paper was 0.202.

Determinations of C'_{H50} performed in quadruplicate on the serums of the other 10 normal blood donors produced values that ranged from 0.00278 ml. to 0.00488 ml., with a mean value of 0.00376 ml. and a mean standard deviation of 0.00017 ml. The coefficient of variation was 4.5%, and the mean slope was 0.205.

TABLE 3.—*Correlation of Laboratory Data and Activity of Complement in Patients with Lupus Erythematosus*

Complement, as C'_{H50}	Determination	Patients	Incidence, Per Cent of Tests Performed *							
			Albuminuria, Grade 2 or More	Serum Albumin < 3.5 Gm. per 100 Ml.	Serum Globulin > 3.6 Gm. per 100 Ml.	Sedimentation Rate > 20 Mm. First Hour (Westergren)	Positive Serologic Tests for Syphilis: Flocculation	Positive Serologic Tests for Syphilis: Complement Fixation †	Leucocytes < 5,000 per Cu. Mm.	L. E. Cells Present
< 0.00500 ml.	12	12	16.7	22.2	22.2	66.7	33.3	9.1	50	25
> 0.00500 ml.	15	15	60	73.3	26.7	100	30.8	54.5	73.3	83.3
	25	7	50	88.9	16.7	95.7	50	44.5	65.2	88

* Every test was not performed in conjunction with each determination of complement.
† This also includes anticomplementary results.

Decreased activity of complement, as manifested by an increase in the amount of serum necessary to produce 50% hemolysis (C'_{H50}), was noted in the majority of patients who had lupus erythematosus. In only 8 of these 27 patients was the C'_{H50} less than 0.003745, which was the mean value for C'_{H50} observed in 50 of the normal blood donors. In 15 of the 27 patients, the C'_{H50} was greater than the maximal value encountered in the entire group of 60 normal blood donors. The use of as much as 0.5 ml. of serum from two patients on three occasions did not cause 50% hemolysis.

A summary of laboratory and clinical data on the patients who had disseminated lupus erythematosus is shown in Tables 3, 4, 5, and 6. For analysis, the cases were arbitrarily divided into two groups: (1) 12 cases in which the C'_{H50} of the patient's serum was less than 0.00500 ml., and (2) 15 cases in which the initial C'_{H50} of the patient's serum was greater than 0.00500 ml. The determinations of C'_{H50} in the latter group were split into two subgroups: (*a*) the initial determina-

10. Berkson, J.: Why I Prefer Logits to Probits, Biometrics **7**:327-339, 1951.

11. Dr. Joseph Berkson gave his assistance in the statistical methods used in this study.

TABLE 4.—*Further Correlation of Laboratory Data and Activity of Complement in Patients with Lupus Erythematosus*

Test	Result	Complement (C''_{H50}), Per Cent Incidence	
		< 0.00500 Ml.	> 0.00500 Ml.
Albuminuria	Grade 2 or more	18.2	81.8
	Less than Grade 2	62.5	37.5
Serum albumin	Less than 3.5 gm. per 100 ml.	15.4	84.6
	3.5 gm. or more per 100 ml.	63.6	36.4
Serum globulin	3.7 gm. or more per 100 ml.	33.3	66.7
	Less than 3.7 gm. per 100 ml.	38.9	61.1
Sedimentation rate	Greater than 20 mm. in one hour	34.8	65.2
	20 mm. or less in one hour	100.0	0.0
Serologic tests for syphilis			
Flocculation	Positive	50.0	50.0
	Negative	47.1	52.9
Complement fixation	Positive or anticomplementary	14.3	85.7
	Negative	66.7	33.3
Leucocytes	Less than 5,000 per $mm.^3$	35.2	64.8
	5,000 or more per $mm.^3$	60.0	40.0
L. E. cells	Positive	16.7	83.3
	Negative	75.0	25.0

TABLE 5.—*Correlation of Clinical Data and Activity of Complement for Patients with Lupus Erythematosus*

Complement, as C''_{H50}	Determinations	Patients	Incidence at Time of Determination of Complement, Per Cent			
			Cutaneous Lesions	Arthralgias	Temperature, Degrees F.	
					1 to 2	> 2
< 0.00500 ml.	12	12	58.3	50	41.6	0
> 0.00500 ml.	15	15	86.6	60	26.7	46.7
	25	7	88	60	20	68

TABLE 6.—*Further Correlation of Clinical Data and Activity of Complement for Patients with Lupus Erythematosus*

Condition	Complement (C''_{H50}), Per Cent Incidence	
	< 0.00500 Ml.	> 0.00500 Ml.
Cutaneous lesions		
Present	35.0	65.0
Absent	71.4	28.6
Arthralgias		
Present	40.0	60.0
Absent	50.0	50.0
Temperature, degrees F.		
0	63.6	36.4
1 to 2	55.5	44.5
More than 2	0.0	100.0

tions of C'_{H50} for all these 15 patients, and (*b*) all determinations of C'_{H50} made for 7 of these patients for whom the values were greater than 0.00500 ml.; 25 determinations were included in the latter group.

Decreased amounts of complement in the serum of patients who had disseminated lupus erythematosus were associated with albuminuria, decrease in serum albumin, increased erythrocytic sedimentation rates, positive or anticomplementary results of complement fixation tests for syphilis, leucopenia, Hargraves' L.E. cells, cutaneous lesions, and fever (Tables 3, 4, 5, and 6). Normal values for serum complement were noted in patients who had lupus erythematosus when such associated findings were absent.

Decreased values for serum albumin were noteworthy; values as low as 1.3 gm. per 100 ml. were observed. Increase in the sedimentation rate of erythrocytes, as commonly noted in lupus erythematosus, was also present in this group of cases. Sedimentation rates as great as 157 mm. in the first hour (Westergren method) were encountered. Leucopenia was a prominent feature in many of the cases in this study, with leucocyte counts ranging as low as 1,700 per cubic millimeter of blood. In only a single case was the leucocyte count more than 10,000; in this instance, the patient, who had peritonitis, displayed a leucocyte count of 18,000.

In one case, a definite history of syphilis accounted for the positive results of the serologic tests for syphilis. No definite history or clinical evidence of syphilis other than the positive results of serologic tests was noted in any of the other cases, although in several the presence of positive results of serologic tests for syphilis apparently was the first manifestation of disseminated lupus erythematosus; in such cases, the patients had received antisyphilitic therapy elsewhere, without change in the result of these tests.

COMMENT

The use of the spectrophotometer to measure the degree of hemolysis [12] and the application of the Von Krogh absorption equation (logistic) [13] to assist in the accurate interpolation of values for C'_{H50} have resulted in a reproducible quantitative method as evidenced by the previously mentioned coefficient of variability of 4.5% in C'_{H50} determinations in quadruplicate on 10 blood donors.

It is generally accepted that albuminuria, hypoalbuminemia, hyperglobulinemia, increase in erythrocytic sedimentation rates, positive results of serologic tests for syphilis, anticomplementary results of complement fixation tests, leucopenia, the presence of L.E. cells in the sternal marrow or peripheral blood, cutaneous lesions, arthralgias, and fever are associated with exacerbations of disseminated lupus erythematosus.[14] The data in this study demonstrate a correlation of C'_{H50} with the grade of albuminuria, levels of serum albumin, erythrocyte sedimentation rates, results of complement fixation tests for syphilis, leucocyte counts, and the presence

12. Mayer, and others.[4] Kent, and others.[5]

13. Von Krogh, M.: Colloidal Chemistry and Immunology, J. Infect. Dis. **19**:452-477 (Sept.) 1916.

14. Baehr, G.: Disseminated Lupus Erythematosus, in A Textbook of Medicine, edited by R. L. Cecil; W. McDermott, and H. G. Wolff, Ed. 7, Philadelphia, W. B. Saunders Company, 1947, pp. 510-515. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948, pp. 944-963.

of L.E. cells, cutaneous lesions, and fever. Apparently no such correlation exists with the levels of serum globulin, results of flocculation tests for syphilis, and the presence of arthralgias.

Comparison of the mean slopes (1/n) in the various groups (Table 7) shows a decrease in the slope when $C'_{1\,50}$ is greater than 0.00500 ml. This is evidence of the presence of an anticomplementary factor in these serums.[15] The most obvious explanation is that the $C'_{1\,50}$ and the anticomplementary titer of a serum are indirectly proportional and the increase in $C'_{1\,50}$ with exacerbations of disseminated lupus erythematosus is caused by an increase in some anticomplementary factor in the serum. However, this would appear to be refuted by the fact that in several cases great increase in $C'_{1\,50}$ was associated with a decrease in 1/n and negative

TABLE 7.—*Comparison of the Mean Slope (1/n) of the Plots of Log* $\frac{Y}{1-Y}$ *Against Log X in Blood Donors and in Patients with Lupus Erythematosus*

Complement, as $C''_{1\,50}$	Determinations	Persons		Mean Slope (1/n)
		Blood Donors	Patients with Lupus Erythematosus	
< 0.00500 ml	50	50	..	0.202
	40	40	..	0.205
	12	..	12	0.192
> 0.00500 ml	15	..	15	0.151
	25	..	7	0.169

results of complement fixation tests for syphilis. Jordan[16] stated that no direct connection exists between complementary and anticomplementary powers in a given serum.

Complement may act in either of two ways in the intensification of immune mechanisms. Complement may actually dissolve the bacteria-antibody complex or it may increase the phagocytic activity of leucocytes on this complex by both opsonic and chemotactic activity. Complement is not a single constituent of serum but is a complex of at least four distinct factors: C'1, C'2, C'3, and C'4. All four components apparently are necessary for the destruction of cells by lysis.[2] Evidence points to the identity of the complement concerned in bactericidal and in hemolytic reactions.[17] It is still a matter of uncertainty whether only three or all four components are needed for stimulation of phagocytosis. It is also uncertain whether all four components are removed quantitatively when brought into antigen-antibody combinations.[2] Removal of C'1, C'2, or C'4 results in a loss of opsonic activity

15. Fischel, E. E.; Pauli, R. H., and Lesh, J.: Serological Studies in Rheumatic Fever: Serum Complement in the Rheumatic State, J. Clin. Invest. **28**:1172-1181 (Sept., Pt. 2) 1949.

16. Jordan, F. L. J.: Clinical Investigations About Complement, Acta med. scandinav. **111**:372-395, 1942.

17. Dozois, T. F.; Seifter, S., and Ecker, E. E.: Immunochemical Studies on Human Serum: The Role of Human Complement in Bactericidal Phenomena, J. Immunol. **47**:215-229 (Sept.) 1943.

concomitant with a loss of hemolytic activity.[18] Mayer and Croft [19] obtained evidence from kinetic studies which demonstrated that antibody resembles an enzyme, whereas complement operates as a cofactor that is used up in the process. Delaunay and Pagès [20] stated that chemotaxis appears to be impossible in the absence of complement, and that phagocytosis is enhanced by its presence.

Efforts to determine the cause of disseminated lupus erythematosus have been inconclusive. Although more and more evidence is being accumulated to support the belief that disseminated lupus erythematosus is an allergic phenomenon, its mechanism has not been elucidated. Fox [1a] presented a case in which presumptive evidence was present that a foreign protein was the irritating factor and perhaps the actual cause. Welsh [1d] showed that streptococci isolated from various patients who had lupus erythematosus were serologically identical; he demonstrated a specific relationship between these patients and this Streptococcus. He further suggested that disseminated lupus erythematosus must be the result of a reaction in a sensitized person to the organism itself or to the products of the growth of the organism.

Teilum [21] considered that hyperglobulinemia, periarterial fibrosis of the spleen, and the wire-loop lesions of the glomeruli in disseminated lupus erythematosus are expressions of a primary allergic hyperglobulinosis in the reticuloendothelial system. Further evidence is offered by the similar patterns of symptoms in disseminated lupus erythematosus and in serum sickness. Fox [1a] was of the opinion that the differences suggest a variation of degree rather than of kind. Criep [22] considered that some evidence existed that disseminated lupus erythematosus may be closely related to the phenomena in hypersensitiveness. It is well known that sensitization in lupus erythematosus may be aided by exposure to sunlight and by the presence of menses, pregnancy, infection, shock, or emotional crises.

On the basis of certain experimental and clinical evidence, Coburn and Moore [23] postulated that damage to tissues may follow simple bacterial infection and result in the presence of an autoantigen in a peculiar host. Gear's [24] hypothesis of the pathogenesis of blackwater fever can be combined with Welsh's work on lupus erythematosus to explain the pathogenesis of lupus erythematosus in that streptococci plus certain tissue of a peculiar host result in an autoantigen. This autoantigen plus reticuloendothelial cells produces an antibody; combination of this autoantigen

18. Ecker, E. E., and Lopez-Castro, G.: Complement and Opsonic Activities of Fresh Human Sera, J. Immunol. **55**:169-181 (Feb.) 1947.

19. Mayer, M. M., and Croft, C. C.: On the Kinetics of Hemolysis by Antibody and Complement, Federation Proc. **7**:308 (March) 1948.

20. Delaunay, A., and Pagès, J.: Le complément dans la physiologie du leucocyte, Rev. immunol. **10**:33-44, 1946.

21. Teilum, G.: Hyperglobulinemia, Periarterial Fibrosis of the Spleen, and the Wire Loop Lesion in Disseminated Lupus Erythematosus in Relation to Allergic Pathogenesis, Am. J. Path. **24**:409-427 (March) 1948.

22. Criep, L. H.: Collagen Disease: Its Relation to Hypersensitiveness, J. Allergy **20**:116-132 (March) 1949.

23. Coburn, A. F., and Moore, D. H.: The Plasma Proteins in Disseminated Lupus Erythematosus, Bull. Johns Hopkins Hosp. **73**:196-221 (Sept.) 1943.

24. Gear, J.: Autoantigens and Autoantibodies in the Pathogenesis of Disease with Special Reference to Blackwater Fever, Tr. Roy. Soc. Trop. Med. & Hyg. **39**:301-314 (Feb.) 1946.

with the antibody produces the clinical manifestations of disseminated lupus erythematosus. In this event, fixation of complement may occur with resultant diminution in the hemolytic activity of the serum of a patient who has disseminated lupus erythematosus during an exacerbation of the disease.

Bordet and Gengou [25] demonstrated by in vitro methods that diminution of circulating complement occurred in certain experimental antigen-antibody reactions; Friedberger and Hartoch [26] made similar observations in vivo. Diminution of complement has been reported in some cases of serum sickness.[27] One patient who had a serum-sickness type of reaction to penicillin exhibited a C'_{H50} of 0.00024 ml.

Ecker and associates,[28] in a survey of complement in infectious diseases in man, arrived at the conclusion that many of the apparent contradictions and inconsistencies encountered in the literature can be attributed to lack of uniform technique in the assay of complement and to inadequate definition of the limits of normal and abnormal values for complement.

Processes other than fixation by antigen-antibody aggregates may cause diminution in the amount of complement. Decreased production of complement is said to occur in hepatic disease [29] and in terminal illnesses.[30] Also, complement apparently may be decreased by the presence of inhibitory or anticomplementary substances in the serum.

SUMMARY AND CONCLUSIONS

Quantitative spectrophotometric studies were made of the hemolytic activity of complement in serum from 60 healthy blood donors and from 27 patients who had disseminated (systemic) lupus erythematosus. Activity of complement was measured by determination of the amount of serum necessary to produce 50% hemolysis (C'_{H50}) of sheep erythrocytes. The mean C'_{H50} on serums of 50 of the blood donors was 0.003745 ml. The mean C'_{H50} when quadruplicate determinations were done on serum from 10 blood donors was 0.00376 ml. In 12 of the 27 patients who had disseminated lupus erythematosus, the C'_{H50} was less than 0.00500 ml. on the initial determination; in 15, the C'_{H50} was greater than 0.00500 ml. This indicated lessened activity of complement because of the greater than normal amount of serum needed to produce 50% hemolysis.

A definite correlation was noted between activity of complement and albuminuria, values for serum albumin, erythrocytic sedimentation rates, results of complement fixation tests for syphilis, leucocyte counts, demonstration of L.E. cells, cutaneous

25. Bordet, J., and Gengou, O.: Sur l'existence de substances sensibilisatrices dans la plupart des sérums antimicrobiens, Ann. Inst. Pasteur **15**:289-302 (May) 1901.

26. Friedberger, E., and Hartoch, O.: Über das Verhalten des Komplements bei der aktiven und passiven Anaphylaxie, Ztschr. Immunitätsforsch. **3**:581-638 (Oct. 27) 1909.

27. Fischel, E. E., cited by Fischel and others.[15] Rutstein, D. D., and Walker, W. H.: Complement Activity in Pneumonia, J. Clin. Invest. **21**:347-352 (May) 1942.

28. Ecker, E. E.; Seifter, S.; Dozois, T. F., and Barr, L. M.: Complement in Infectious Disease in Man, J. Clin. Invest. **25**:800-808 (Nov.) 1946.

29. Ecker, E. E.; Seifter, S., and Dozois, T. F.: Human Complement, J. Lab. & Clin. Med. **30**:39-50 (Jan.) 1945.

30. Longcope, W. T.: Study of the Bacteriolytic Serum-Complements in Disease: A Contribution to Our Knowledge of Terminal and Other Infections, J. Hyg. **3**:28-51 (Jan.) 1903.

lesions, and fever. No correlation was noted between C'_{H50} and values for serum globulin, results of flocculation tests for syphilis, and arthralgias.

Evidence of the presence of some anticomplementary substance was noted in these serums; however, this does not appear to account for the entire increase in C'_{H50} in these cases.

Such factors in patients who have disseminated lupus erythematosus as the decrease in activity of complement against sensitized sheep erythrocytes concomitant with exacerbation of the disease, the anticomplementary results of complement fixation tests for syphilis, the presence of hyperglobulinemia, and the increased reactivity to foreign proteins, surgical procedures, menses, pregnancy, shock, and emotional crises are all compatible with the theory that disseminated lupus erythematosus is a state of hypersensitiveness.

It is concluded that the serum of healthy persons displays activity of complement that is within a comparatively narrow range, and, furthermore, that this hemolytic activity of complement is correlated with the activity of disseminated lupus erythematosus.

FLUORESCENCE OF MICROSPORUM AUDOUINI-INFECTED HAIR

I. Chemical and Spectroscopic Studies

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SINCE 1944 the eastern portion of the United States has been afflicted with an epidemic of tinea capitis among children below the age of puberty. The predominating organism cultured from infected patients has been the Microsporum audouini, and the large number of cases available in our clinic stimulated us to undertake a study of some of the characteristics of this fungus.

There are many features of the course of M. audouini infection of the hair which require explanation. In this series of experiments we have attempted to determine the chemical nature of the substance which produces a greenish fluorescence when exposed to the Wood light.

STUDIES ON FLUORESCENT MATERIAL IN MICROSPORUM AUDOUINI INFECTED HAIR

The nature of fluorescent substance contained in infected hair has occasioned great interest since the discovery of this phenomenon by Margarot and Deveze [1] in 1925. The term fluorescence was first applied to chemical substances by Stokes [2] in 1852. He derived the term from fluorospar because this substance also exhibited the same phenomenon. In this portion of our investigation studies have been conducted to determine something of the nature of this fluorescent material by chemical reactions and spectrophotometry.

CHEMISTRY OF FLUORESCENT MATERIAL

Felsher [3] noted that the fluorescence changed color at various hydrogen ion concentrations and stated that it was due to a fluorescent indicator substance. He also stated that various ions quenched the fluorescence without affecting the viability of the fungus.

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Part I of the paper read before the Section on Dermatology and Syphilology at the One Hundred and First Annual Session of the American Medical Association, Chicago, June 10, 1952.

1. Margarot, J., and Deveze, P.: Aspect de quelques dermatoses en luminère ultraparaviolette: Note preliminaire, Bull. Soc. sc. méd. et biol. Montpellier **6**:375, 1925.

2. Stokes, G., cited by Pringsheim, P., and Vogel, M.: Luminescence of Liquids and Solids, New York, Interscience Publishers, Inc., 1943.

3. Felsher Z.: Observations on the Fluorescent Material in Hairs Infected by Microsporon in Tinea Capitis, J. Invest. Dermat. **12**:139, 1949.

The fluorescent substance may be readily extracted from the infected hair by boiling with distilled water. The material is very slightly soluble in 95% alcohol and dioxane. It is insoluble in N/10 hydrochloric acid, ether, carbon tetrachloride, acetone, and carbon disulfide. Attempts to purify the substance for spectroscopic examination were complicated by the fact that the fluorescent substance is not adsorbed from the aqueous solution by aluminum oxide, talc, aluminum silicate (fullers' earth), and filter paper. Because of this, chromatographic studies were not conducted. Ethyl acetate, ether, chloroform, carbon disulfide, carbon tetrachloride, and other fat solvents do not extract the substance from the aqueous solution.

The fluorescent substance is destroyed by strong acids and strong bases. The pH fluorescent curve (Chart 1) exhibits a maximum intensity at pH 6.5 and minimal intensity at pH 3 and pH 9.5

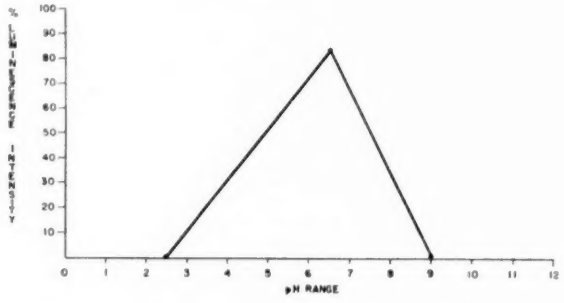

Chart 1.—pH range of fluorescence. Fluorescence is most intense at pH 6.5.

The pigment is a small molecule which dialyzes readily through Cellophane. It dries to a fine powder which retains fluorescence. The material is not affected by prolonged exposure to bactericidal light of 2,537 A.

Infiltration of M. audouini produces a chemical reaction which involves the hair pigment. To prove this, infected hair was treated with ethyl ether for one hour to remove the surface oils, then it was placed in a tube and boiled with distilled water. The fluorescent substance was completely extracted by the water, and the remaining hair was found to be dull gray in color. Control studies were conducted with noninfected hair, and the normal pigment was not affected.

The fluorescent substance was demonstrated to be reversibly oxidizable by the addition of sodium dithionate to an aqueous solution. When the reagent was first added and the solution agitated, the fluorescence disappeared, but on prolonged shaking with oxygen it reappeared.

In order to purify the substance for spectroscopic examination, a mixture of aluminum oxide, aluminum silicate, and talc was added to an aqueous extract of infected hair to remove all other impurities. The solution was then filtered and evaporated to a dry powder which still retained the characteristic fluorescence.

SPECTROSCOPIC STUDIES ON FLUORESCENT SUBSTANCE

A fixed characteristic of any substance is its ability to absorb electromagnetic radiations of a specific wave length and form a characteristic pattern. A color is a specific absorption spectrum whose intensity varies in proportion to the absorbing substance. White light is a combination of all the colors of the visible spectrum, and therefore an analysis of the absorption spectrum frequently gives information as to the chemical nature of the substance under consideration. Absorption spectra occur in both the ultraviolet and the infrared ranges of the electromagnetic spectrum and have been widely used in both chemistry and physics for the identification of specific substances. Stokes [2] stated that irradiated matter becomes self-luminous and that the wave length of the emitted light need not be contained in the incident beam. This same investigator stated that fluorescent light always has a greater wave length than the exciting light and its corresponding absorption bands.

A gross comparative study of fluorescent organic materials was conducted to determine those which most closely resembled the color emitted by M. audouini-infected hair when exposed to the Wood light. Dihydrocollidine, a substance found in decaying fish, emitted a greenish-blue color which approximated that of infected hair. However, when a spectrographic study of fluorescent spectra was made, gross differences were noted in the bands. In instances in which the fluorescent spectrum exhibits characteristic lines, spectrographic observation may be of special use in identification and as an adjunct in purification procedures.

METHODS AND MATERIALS

In order to determine the fluorescent spectra of the substances examined and compared, a Gaertner small quartz spectrograph was used and the recordings were made on panchromatic photographic film or plate. The slit width was placed at *2* on the Vernier scale, and the substances to be examined were placed 37.7 cm. from the slit. The light emitted from the test material was focused on the spectrograph slit by means of a small glass lens (focal distance 11.25 cm.) which was placed 11.25 cm. from the slit. The substances were irradiated with two sources of light, a Wood light with a range of 3,300 to 4,000 A, and a low pressure mercury arc light of 2,537 A. The substances to be examined were placed in quartz or Cellophane tubes which transmit light of all wave lengths. The light was carefully focused on the prism and a fluorescent plate, which was then replaced with the photographic plate. Exposures to three to five minutes were found to be the most satisfactory for recordings.

Comparative studies were conducted with fluorescein, dihydrocollidine, distilled water, protoporphyrin, riboflavin, infected hair, noninfected hair of various types and colors, and a solution of fluorescent substance extracted from M. audouini-infected hair with water. Ultraviolet absorption spectra of water solution of the fluorescent substances were made with use of the Beckman quartz spectrophotometer.

RESULTS

Spectrographic studies of the substance extracted from infected hair with water indicated that the substance had a fluorescent spectrum with a wide distinct band ranging from 4,543 Å to 5,490 Å (Chart 2). The maximum was at 4,902 Å. Infected hairs show a luminescent spectrum of the fluorescent material, but there is superimposed on this the fluorescent spectrum of nonpigmented hair which tends to obscure the spectrum of the substance itself (Chart 3). Gray hair and infected hair have almost identical fluorescent spectra because of melanin, which quenches or absorbs the light rays (Chart 4). In black or brown hair most of the light is

absorbed by the pigment. Dihydrocollidine, fluorescein, and protoporphyrin were found to have characteristic spectra, but these did not coincide with that of the pigment of infected hair.

The ultraviolet absorption spectrum (Chart 5) did not show absorption bands characteristic of any specific substance.

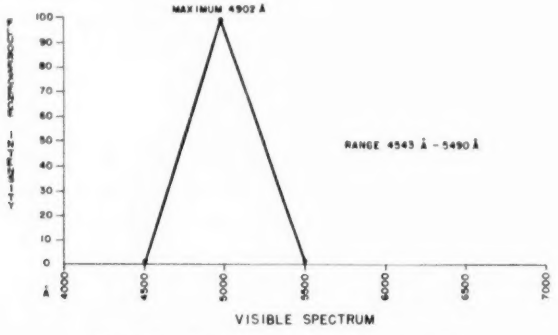

Chart 2.—Angstrom range of fluorescence.

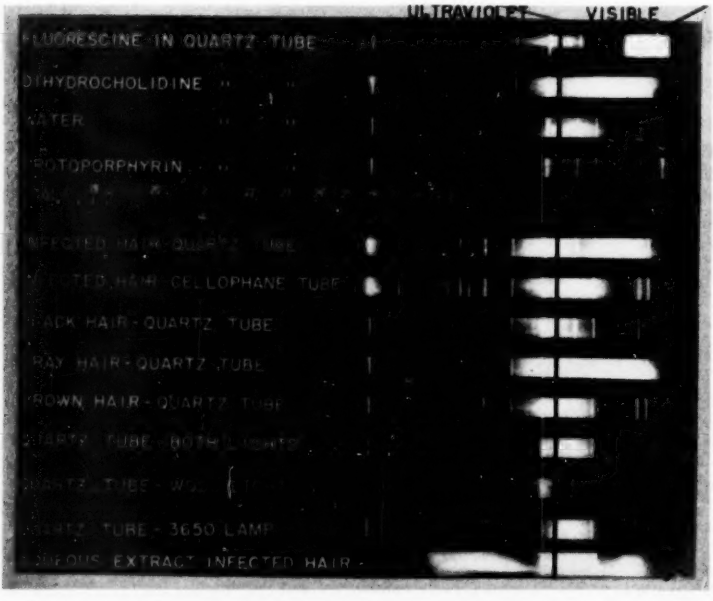

Chart 3.—Comparative fluorescent spectroscopic studies of infected hair with other materials.

INFRARED ABSORPTION SPECTROSCOPIC STUDIES ON FLUORESCENT SUBSTANCE

An aqueous solution of fluorescent substance extracted from hair infected with M. audouini was treated with talc, aluminum oxide, and aluminum silicate in order to remove all impurities. The mixture was filtered, and the filtrate was dried to a white powder by freezing it on the walls of the flask with liquid nitrogen and placing

it on a vacuum line at a temperature of 10 C to 15 C under a pressure of less than 1 μ for 20 hours. From 8 to 10 mg. of this powder was mulled in mineral oil and a similar amount of hexachlorobutadiene, and several curves were determined for each, more or less material being used in the beam in different parts of the spectrum

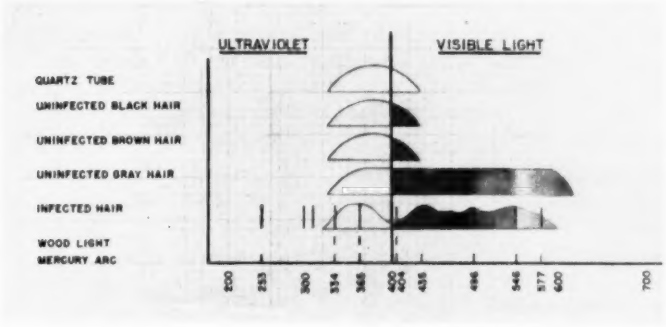

Chart 4.—Transposition of luminescence spectra of hair to colors of visible spectrum. Sources of light: Wood light and bactericidal mercury arc.

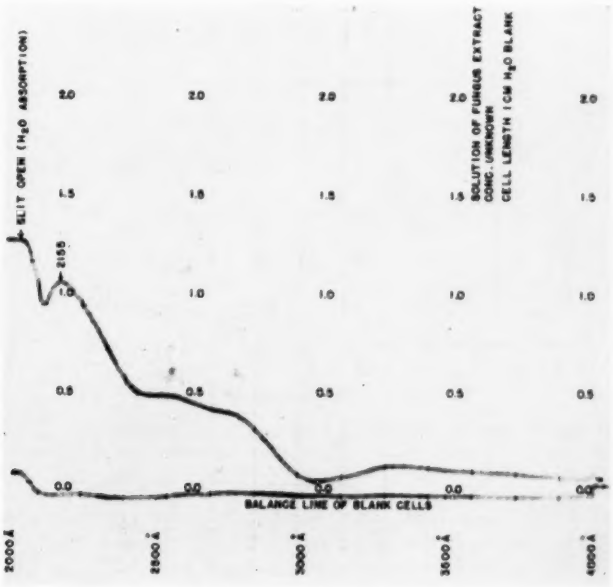

Chart 5.—Ultraviolet absorption spectrum. This does not show absorption bands characteristic of any specific substance.

for optimum results. A Perkin Elmer Model 21 spectrophotometer with a sodium chloride prism was used in this study. This spectrum (Chart 6) is a composite of spectra obtained in mineral oil and hexachlorobutadiene; therefore, there are no solvent or mulling agent bands included.

The strong broad band at 3,270 cm.$^{-1}$ indicates a stretching mode of –OH or =NH very strongly hydrogen bonded, and the small band at 3,050 indicates the group –CONH–. The frequency is lower than the usual peptide band, but lactams occasionally have such a low –NH stretching band. The band near 1,900 is often found in the amino acids, and the strong band at 1,650 is characteristic of strongly bonded C=O generally of carboxylate or amide groups. All peptides show a strong band at about 1,650, which has been attributed to =NH deformation; however, certain lactams also show strong absorption near 1,250 or 1,300 cm.$^{-1}$ as in this

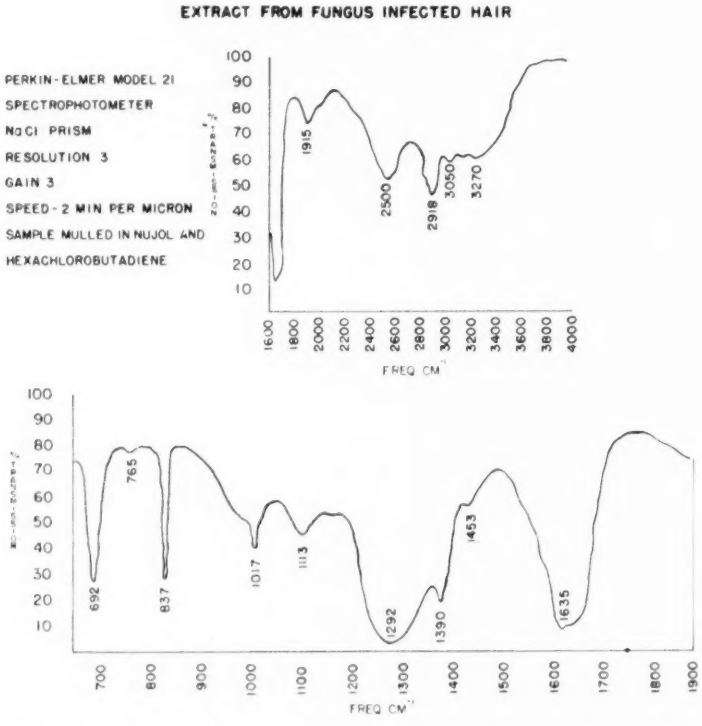

Chart 6.—Infrared absorption spectrum. This recording contains relatively few absorption bands and thus is indicative of a small molecule resembling a peptide which contains a —CONH group, and —OH group, a CH_3 group, and an =NH group.

case. The weakness of the 1,450 band would indicate the presence of $=CH_3$. The band near 700 is also characteristic of the –CONH– group.

This spectrum contains comparatively few bands; this indicates that the substance is a relatively small molecule, and the conclusion is that it resembles a peptide which contains a –CONH– group, an –OH group, a CH_3 group, and an =NH group.

SUMMARY AND CONCLUSIONS

The fluorescent substance may be extracted from infected hair by boiling in distilled water. It dries to a fine white powder which retains fluorescence when exposed to the Wood light. The substance is not adsorbed from aqueous solution

by aluminum silicate, aluminum oxide, talc, or filter paper, and is not extracted from aqueous solution by the usual organic fat solvents. The substance is destroyed by strong acids and bases, and has a maximum intensity at pH 6.5. Infiltration of M. audouini produces a chemical reaction which involves the hair pigment, and when the fluorescent material is extracted the remaining hair is lusterless and dull gray in color. The fluorescent material is reversibly oxidizable.

Spectrographic studies indicate that the fluorescent substance has a wide distinct band with maximum at 4,902 A. Gray hair and infected hair have almost identical spectra because of the absence of melanin, which absorbs light rays. Ultraviolet absorption spectra did not show bands characteristic of any specific substance. The infrared absorption spectra indicate that the substance is a small molecule which resembles a peptide and contains a –CONH– group, an –OH group, CH_3 group, and a =NH group. The results obtained in this series of experiments with infrared absorption indicate that the exact chemical composition may be found with this method. Further studies must be conducted with this same technique.

CAPILLARY MICROSCOPIC EXAMINATION IN SKIN DISEASES

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SOME FEATURES of a dermatosis may be recognized by direct observation of the skin, and a magnifying glass may help in seeing more of the detail. Epidermoscopy [1] and diascopy [2] may give additional help in the study of certain skin lesions. Coloroscopy is a new technique for studying microscopic organisms and human tissues with colored polarized light. Since these methods of inspection permit of superficial study only, microscopic examination is still the best procedure to determine the pathologic changes in the skin. It is, however, a study of dead tissue and has its limitations, according to histopathologists.[3]

A direct study of the pathologic and physiologic changes in the living skin under natural conditions may be done by means of capillary microscopy. This is a method of observing the superficial cutaneous vessels through a microscope under direct incident illumination after the skin has been made transparent by application of a drop of immersion oil to the field to be examined. This technique is especially applicable to the examination of the individual lesions in skin disease.

HISTORY

Capillary microscopy is not a new diagnostic procedure, since it was attempted by Johan Christophorus Kolhaus as early as 1663. He reported that he could see with the help of a "microscope" small vessels in the nail fold of man. In 1897, Karl Hueter reported his studies of the capillaries in the lower lip with the aid of a magnifying glass and artificial light, which was the first reported capillary microscopic examination in human beings. Unna applied oil on the skin to make it transparent for the study of lupus vulgaris, and Lombar was the first to report the use

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1. Sulzberger, M. B.; Herrmann, F.; Keller, R., and Pisha, B. V.: Studies of Sweating: III. Experimental Factors Influencing the Function of the Sweat Ducts (A Preliminary Report), J. Invest. Dermat. **14**:91-111 (Feb.) 1950. Goldman, L.: Some Investigative Studies of Pigmented Nevi With Cutaneous Microscopy, ibid. **16**:407-426 (June) 1951. Goldman, L., and Younker, W.: Studies in Microscopy of the Surface of the Skin: Preliminary Report of Technic, ibid. **9**:11-16 (July) 1947.

2. Epidermoscopy is examination of the cutaneous surface by means of a microscope. Diascopy is examination of skin lesions by means of a special glass plate pressed against the skin.

3. Lever, W. F.: Histopathology of the Skin, Philadelphia, J. B. Lippincott Company, 1949.

of glycerin on the nail folds to make the capillaries more visible (1911). However, it was the internist, Otfried Müller,[4] who, in 1937, introduced this technique as a method for clinical examination. He constructed a portable apparatus which made it possible to examine the entire body. Most of the earlier capillary microscopic examinations had been done in the nail folds[5] and also in the lip,[6] eyes,[7] ear, gingiva,[8] genitalia, and other areas. These studies, however, attempted to diagnose a general or systemic disease from the changes seen in the capillaries, for example, in the nail folds.[9]

The capillary microscopic examination of cutaneous diseases has been used but little according to the reports in the literature, and there seem to have been no attempts at systematic examination.

The interest of one of us (Gilje) in capillary microscopic examination was aroused some years ago when studies were made on the vascular supply of the borders of leg ulcers.[10] In 1947, one of us (Gilje) began the capillary microscopic study of cutaneous disease, attempting to correlate the findings of capillary microscopy with the clinical and histologic findings, and this report is a continuation of the previous work.[11] In addition to relating the characteristic findings in some of the cutaneous diseases, we shall describe the improved technique for capillary microscopic examination, photography in black and white, and color, and the taking of motion pictures.

4. Müller, O.: Die feinsten Blutgefässe des Menschen in gesunden und kranken Tagen: Zur normalen Anatomie und Physiologie sowie allgemeinen Pathologie des feinsten Gefässabschnittes beim Menschen, Vol. 1, 1937; Die feinsten Blutgefässe des Menschen in gesunden und kranken Tagen: Zur speziellen Pathologie des feinsten Gefässabschnittes beim Menschen, Vol. 2, 1939, Stuttgart, Ferdinand Enke Verlag.

5. Hauptmann, A.: Capillaries in Finger Nail Fold in Patients With Neurosis, Epilepsy and Migraine, Arch. Neurol. & Psychiat. **56**:631-642 (Dec.) 1946. Roth, G. M.: Nailfold Capillaries in Man, in Allen, E. V.; Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, Philadelphia, W. B. Saunders Company, 1946, pp. 148-164. Brieger, H.: Zur Anwendung der Capillarmikroskopie nach Jaensch-Hoepfner-Wittneben, Klin. Wchnschr. **8**:296-299 (Feb. 12) 1929. Brown, G. E.: The Skin Capillaries in Raynaud's Disease, Arch. Int. Med. **35**:56-73 (Jan.) 1925.

6. Bettmann, S.: Capillarmikroskopische Untersuchungen an der Lippenschleimhaut, Arch. Dermat. u. Syph. **162**:480-516, 1931.

7. Lack, A.; Adolph, W.; Ralston, W.; Leiby, G.; Winsor, T., and Griffith, G.: Biomicroscopy of Conjunctival Vessels in Hypertension: A Capillary "Hypertension Pattern" and the Occurrence of Intravascular Clumping (Sludged Blood) Are Described, Am. Heart J. **38**:654-664 (Nov.) 1949.

8. Parma, K.: Kapillarmikroskopische Untersuchungen bei Schwangeren mit besonderer Berücksichtigung der Zahnfleischkapillaren, Helsinki, Dissertation 1939.

9. Müller, O.: Pathologie des Capillaires Humains, J. de physiol. et de path. gen. **38**:52-62, 1941-1943. Callander, C. L.: Photomicrographic Studies of Morphology of Surface Capillaries in Health and Disease: I. The Anatomy of Normal Surface Capillaries and a Photographic Method of Their Observation and Recording, J. A. M. A. **84**:352-356 (Jan. 31) 1925. Cobb, S.; Cohen, M. E., and Badal, D. W.: Capillaries of Nail Fold in Patients With Neurocirculatory Asthenia (Effort Syndrome, Anxiety Neurosis), Arch. Neurol. & Psychiat. **56**:643-650 (Dec.) 1946. Michael, J. C.: Dermatoscopy, Arch. Dermat. & Syph. **6**:167-178 (Aug.) 1922.

10. Gilje, O.: Ulcus Cruris in Venous Circulatory Disturbances: Investigations of the Etiology, Pathogenesis and Therapy of Leg Ulcers, Acta dermat.-venereol. (Supp. 22) **29**:1-328, 1949.

11. Gilje, O.: Capillary Microscopy in the Differential Diagnosis in Skin Diseases, Acta dermat.-venereol., to be published

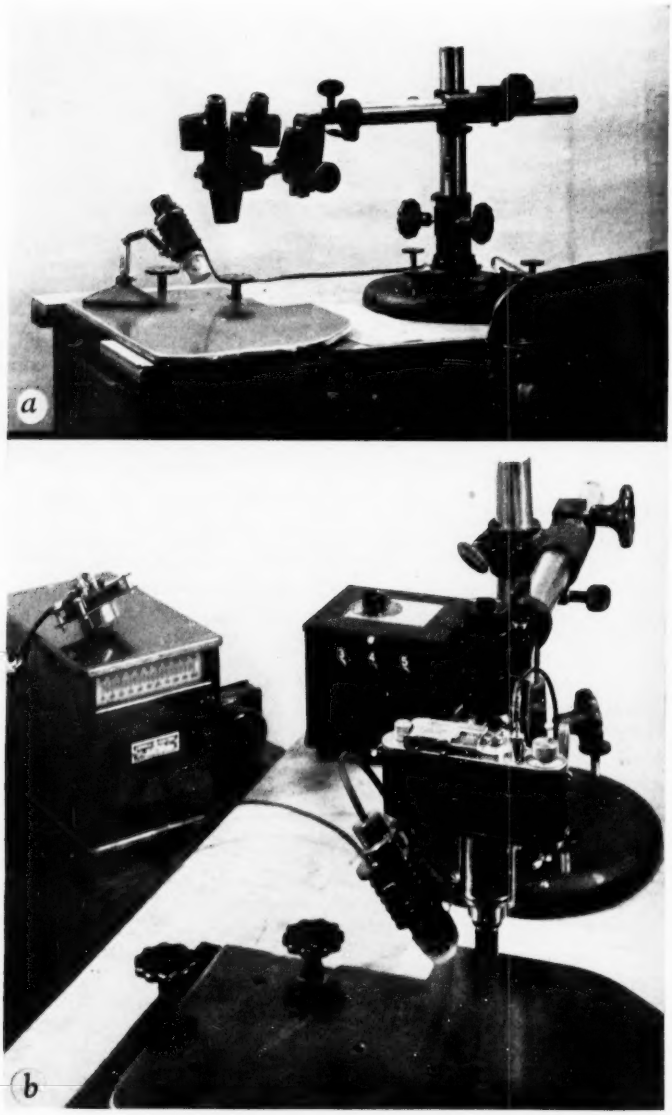

Fig. 1.—(*a*) The binocular capillary microscope, the movable table plate, and the lamp. (*b*) The Zeiss microscope with a Leica camera, photoelectric cell, and galvanometer.

TECHNIQUE

The apparatus used (Fig. 1) consists of a binocular microscope (Spencer), on a movable stand. The microscope is movable in all directions and adjustable at different angles for examination of skin lesions on different parts of the body. The stand should be of heavy construction so as to eliminate vibration. This is especially desirable when the "arm" of the holder is extended as far as possible, as, for example, when examining the skin of the abdomen of a patient lying on the table. The use of the binocular microscope gives greater brightness, better definition, clear visual fields, and stereoscopic vision. The ocular used is 15× and the objectives 3×, 6×, and 8×; since moderate magnification has been found to be more satisfactory the objective 3× is used in most examinations. However, more details can be observed in tissue studied under the higher magnification, but more light and more exact immobilization of the patient are needed when the higher magnifications are used.

The illumination is provided by a regular microscope lamp adjustable to different positions. The lamp used may be either a table model (Fig. 1*a*) or it may be attached to the microscope. The beam of light should fall on the skin at an angle of approximately 45 degrees so that it will penetrate the skin and not be reflected from the surface of the oil. The light should be focused on an area of about 5 mm. in diameter on the skin. The intensity of the light may be regulated by a transformer or a rheostat; although the distance of the lamp from the skin may vary, it is usually 3 to 4 cm.

Since the heat from the lamp will dilate the capillaries, a heat filter is placed inside the lamp housing. In addition, a color filter improves the contrast between the capillaries and the tissue, and we have found that a light-blue or a green filter will give the best field for observation and for taking black-and-white pictures. A combination of green and blue filter also may be satisfactory but requires much more light.

One of the difficulties of capillary microscopy is the immobilization of the part to be examined. It is not difficult to immobilize a finger for nail-fold examination, but a skin lesion on the breast offers difficulties because of the respiratory movements, and both respiration and pulse may interfere with examination of a face lesion. We have used sandbags for the immobilization of different parts of the body, especially the extremities and the head.

The table for the microscope and accessory equipment must be solid and stable so as to minimize the vibrations. This may be accomplished by weighting the table with several pounds of iron. On the end of the table there is a solid metal plate mounted in tracks and movable in two directions by the use of two controls (Fig. 1). This movable part of the table supports the area to be examined and is especially desirable in moving to different fields without disturbing the fixation of the patient.

Most of the examinations can be done with the patient seated in a comfortable chair and the part to be examined placed on the sliding table. However, sometimes it is advisable to have the patient lie on an examining table.

The surface of the skin appears opaque to the naked eye, but in fact it is transparent, and because of its uneven surface the light will be reflected in all directions. The use of a few drops of oil on the skin will smooth the surface and permit the light to penetrate directly. A heavy nondrying immersion oil with high viscosity and low fluorescence has been found to be the most satisfactory (Cargille Scientific Inc., New York). When the bottle of oil is placed in ice water its viscosity is increased, so that it will not run from the field to be examined. Occasionally, it is necessary to surround the oil with a ring of calking compound. Air bubbles in the oil give trouble by reflecting the light, and an easy way to avoid this is to apply the oil with a glass syringe with a small plastic tube about 15 cm. long. The fluorescence may be difficult to eliminate and some examiners have used a cover glass on the oil to avoid it, but we have not found that necessary.

The transparency of the skin varies and depends on the thickness of the skin, hyperkeratosis, edema, pigmentation, and age of the patient. The transparency may be improved by washing the skin lesion with oil and ether. The light in the examining room should be dim for better observation in the microscope.

When examining a histologic section, a vertical section of the skin is seen, while in capillary microscopy a "bird's eye" view is obtained. Usually one can see through all the layers of the epidermis, down into the stratum papillare, and in some cases, down into the stratum reticulare

with the subpapillary ridges of vessels. In some areas the papillae are arranged in rows, while in others they show a ring-like formation. The arterioles forming the subcutaneous plexus send branches toward the papillary layer to form the subpapillary plexus, and from this plexus the fine loops protrude up into the papillae, with one or more loops in each papilla. In the surface of the skin, the conical papillae are mostly arranged vertically and appear as small round or oval formations in the skin (Fig. 2*a*). In the center of some of the papillae, the tips of the capillaries are apparent. At the nail fold, the papillae are arranged horizontally, and the capillaries therefore will be seen in profile (Fig. 2*b*).

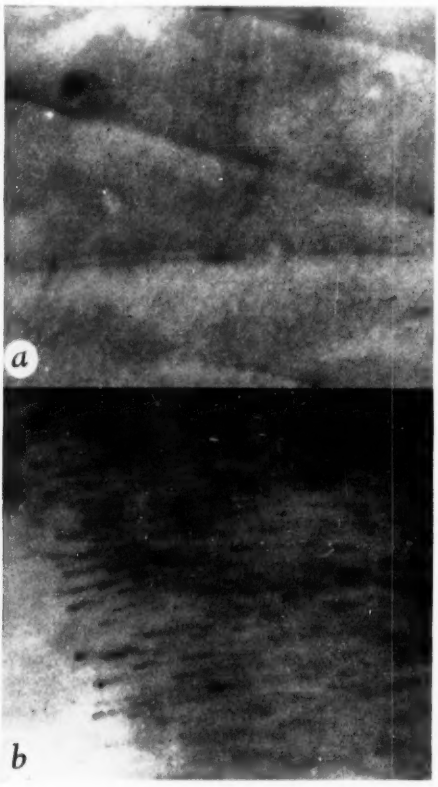

Fig. 2.—(*a*) Normal skin on the back of a hand. Note the lighter round top of the papillae, in the center of which there is a capillary tip. (*b*) Normal nail-fold capillaries. Hairpin-shaped capillaries seen in profile.

The normal capillary loops are usually hairpin-shaped, with a thinner arterial limb and a broader venous limb and between them the so-called crest. Numerous variations of the capillaries as to size, number, shape, and direction can be seen, in addition to elongation of the loops, narrowing or dilatation of the lumen, and increased looping or tortuosity. These variations are usually seen in the crest, although they may be noted in the arterial or the venous limb, and appear in the form of corkscrew, onion, spiral, curls, or coils (like the wire in an electric globe), gable, spindle, spirochete-like forms, and so forth.

The blood flow shows variations in speed, color, and in the column of the blood. Intravascular clumping of the erythrocytes gives a granular blood stream, varying from fine granular to

almost complete clumping of erythrocytes (sludging).[12] Vacant areas in the column of blood are sometimes seen, which presumably may be leucocytes. The blood stream in the subpapillary layer also can be followed and studied in some pathologic situations.

During examination variations in the capillary microscopic picture may be attributed to the location of the area under examination, the age of the patient, his constitution, seasonal variation, the room temperature, and even the time of examination. These factors, however, play a minor role in this study, although they should be kept in mind.

PHOTOGRAPHY

Observations made with the aid of the capillary microscope may be recorded photographically in black and white or in colored prints and motion pictures.

The difficulty with capillary microscopic photography is first the immobilization of the patient. In addition to the movement of the area under examination, it is necessary to consider the almost constant motion of the vessels themselves, such as their contraction and dilatation.[13] A short exposure of about 1/30 second will eliminate most of the movements. However, to obtain short exposures, a bright light is needed. The light source for photography is the same as for microscopic observation, except that the light intensity may be increased many times during the exposure by means of a foot switch and rheostat. A fast film may be used, such as 35 mm. Super XX and Plus X with exposure time 1/40 to 1/30 second.

With the previously mentioned microscope, a 10× ocular and objectives 3.5× and 2.2× have been used. By measuring the light through the microscope with a photoelectric cell, we have found that the light intensity to the film depends not only on the magnifying power of the objective lens but also on the diameter of the lens. Lately, we have changed over to other objectives with greater numerical aperture, Seibert P. A. 4-8×, which gives magnification 4×, or an objective P. B. 7-11, with the magnification about 6×. The camera tube reduces the magnification one-half, so that, for example, the objective 4-8× will give 2½× magnification on the film.

Subsequently, use was made of a Zeiss unit with large reflecting prism, fitted with an adjustable eyepiece, and to which is adapted a Leica camera (Fig. 1*b*). The objectives used were usually Seibert P. A. 4-8×, which in this set-up gives a magnification of 9× on the film; P. B. 7-11×, which magnifies 13×; while the objective Zeiss 8× gives a magnification of 17×.

In adjusting this equipment it is essential that the observer focus accurately the cross hairs of the eyepiece. Next, a test object, such as a 2 mm. micrometer scale divided in 0.01 mm. is brought within focus so that the image of the scale appears superimposed on the cross hairs. Then, it is necessary to adjust the camera so that the test object is focused in the plane of the film. This setup has some advantages. The microscope has a larger eyepiece, and it is not necessary to remove the prism during the exposure of the film (as with the first-mentioned microscope). Hence, one is able to observe the living object continuously when taking a picture. The prism is larger, and since there is no ocular in this microscope more light will pass to the film.

The light source for this apparatus may be attached to the microscope tube (Fig. 1*b*) and is mobile in all directions for focusing and adjusting the light. The lamp is a 6.5 volt, 2.75 ampere bulb. The light intensity can be increased during the exposure using a foot switch to raise the voltage momentarily to 10 volts. As the heat from this lamp is intense, it is necessary to use three heat filters. The field to be photographed should be completely illuminated.

By means of a photoelectric cell and a mirror galvanometer the light intensity can be measured before each exposure (Fig. 1*b*). The photoelectric cell is placed on the top of the microscope. Calibration of the film can be done so that one knows the exposure needed for each light intensity.

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12. Knisely, M. H.; Stratman-Thomas, W. K.; Eliot, T. S., and Bloch, E. H.: Knowlesi Malaria in Monkeys; Microscopic Pathological Circulatory Physiology of Rhesus Monkeys During Acute Plasmodium Knowlesi Malaria (a Motion Picture), J. Nat. Malaria Soc. **4**:285-300 (Dec.) 1945. Knisely, M. H.; Bloch, E. H.; Eliot, T. S., and Warner, L.: Sludged Blood, Science **106**:431-440 (Nov. 7) 1947.

13. Duryee, A. W., and Wright, I. S.: Studies of Human Capillaries: Present Day Technique for the Study of Human Capillaries, Am. J. M. Sc. **185**:664-673 (May) 1933.

In our apparatus we have found that a Super XX film requires an exposure time $T = \frac{1}{R \times 5}$ second where R is the reading on the galvanometer. For Kodachrome (Type A) film, we found $T = \frac{1}{R}$, so that if the reading on the galvanometer is 60, the exposure time on Kodachrome (Type A) should be 1/60 second.

CAPILLARY MICROSCOPIC MOTION PICTURES

Capillary microscopic motion pictures are of special interest in skin diseases in which the vascular changes predominate, as for example, dermatomyositis, lupus erythematosus, and acrosclerosis. In taking motion pictures, the same microscope and light are used as for color photography. We have tried two types of "movie camera" with exposure of 16 frames to 32 frames per second, using 16 mm. Kodachrome (Type A) film. The movie camera can be aligned and adjusted to the microscope tube in the same manner as the still camera, except that the movie camera must not be in direct contact with the microscope in order to eliminate vibration.

RESULTS OF STUDY

Capillary microscopy permits study not only of the blood vessels, especially the capillaries, but also of the surrounding structures of the skin. The furrows, ridges, rows of papillae, hair follicles, sweat and sebaceous glands, changes in structure of the skin, and the pigment and its different patterns are available for study. One of us (Gilje) undertook these investigations to compare the capillary microscopic pictures of the individual skin lesions with the clinical and the histopathologic picture. In addition, the nail folds have been studied in those diseases in which they were of special interest.

During the past six years one of us (Gilje) has studied numerous skin diseases under the capillary microscope, in an attempt to formulate the characteristic patterns in these diseases. In this report a few of the classic capillary microscopic pictures will be described, while others will be discussed in a subsequent publication.[14]

Psoriasis.—The capillary microscopic picture as seen in psoriasis is shown in Figure *3a*; in a bright field, the tips of the regularly arranged, uniformly spaced vertical capillary loops are seen. Frequently there is a single capillary loop in each papilla. The tips or crests of the capillary loops are curled up into balls of about equal size, or sometimes they are like the coil in an electric bulb. These "capillary balls" are arranged in rings or linearly, depending on the location of the area studied (Fig. *3a* and *b*). It is these "balls" which cause the typical spotty bleeding when a psoriasis plaque is scraped. In the border or edge of a plaque, the picture is different. The capillaries here slant inward against the plaque in an oblique direction, so that in the microscope they are seen more in profile. The arterial and venous limbs are visible, and the crests are not curled up. The loops are dilated and wider than normal. In a few of them there may be a single curl. In the skin surrounding the plaque the capillaries will be normally shaped but slightly dilated. If the plaque has been treated, very thin long horizontal capillary loops surrounding the plaque are present. In a picture from a treated patient (Fig. *3c*) sometimes there are found in one field these three sorts of capillaries: (*1*) the curled-up type, (*2*) the oblique form, and (*3*) the horizontal form as described in the preceding sentence. In some healing plaques one can see how the capillaries give the impression of being

14. Gilje, O.; Kierland, R. R., and Baldes, E. J.: Capillary Microscopy in Diagnosis of Dermatologic Diseases, unpublished data.

stretched out. They are not so curled up, and they may be thicker and more diffuse (Fig. 3*d*). In the capillary microscopic picture of psoriasis, subpapillary vessels are not seen. The skin ridges and furrows are normal.

Comparing these findings with the histologic picture we note:

One of the first changes in psoriasis is the bulging of the tips of the papilla bodies which could be interpreted to result from prolongation of the rete ridges, causing compression of the bases of the papillae. In acute and early lesions, the capillary bodies in the upper part of the cutis are dilated and filled with erythrocytes and leukocytes.[14]

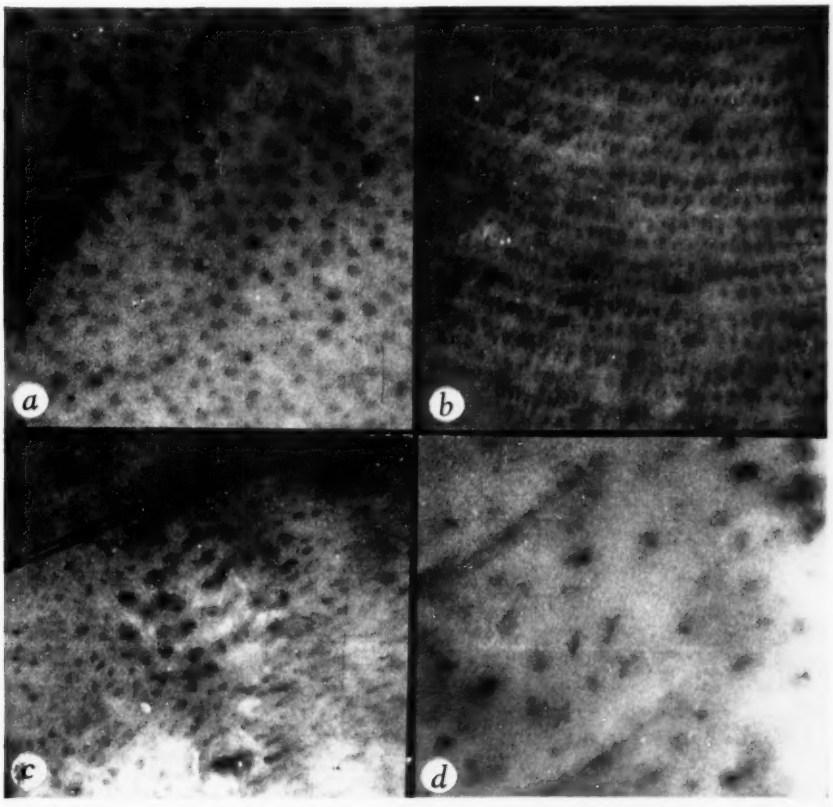

Fig. 3.—(*a*) The capillary microscopic picture in psoriasis. (*b*) Psoriasis on the volar side of a finger. Note the linear arrangement of the capillaries. (*c*) Psoriasis after some treatment. In the center there still are some curled-up capillary loops, while in the periphery the loops are oblique and far out. Some of them are horizontal and thin. (*d*) Psoriasis after two weeks' treatment. The capillaries are not so much curled up as in *c*.

We also compared our findings with what Ormsby and Montgomery[15] found in patients after treatment: "At the border of the lesions, extending well into normal tissue, there was increase of edema and vascular dilatation in the cutis, when before treatment, no appreciable change had been present."

15. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948.

Lichen Planus.—This disease has a characteristic picture in the capillary microscope. There is an irregular central field of varying size and form, like a plateau, surrounded by a border of hairpin-shaped, regularly arranged, straight and slender, slightly looped or twisted capillary loops which slant inward and upward toward the central field. A single papule is seen as a small white or light polygonal prominence, surrounded by a border of elongated and slightly dilated, not curled-up, capillary loops (Fig. 4*a*). More curious is the picture where there are more papules and plaques formed together (Fig. 4*b*). Many varying configurations are seen in that way if the center field is large, and in older plaques there sometimes will be seen a diffuse dark-brownish irregular mass in the middle of the light area. In this mass there sometimes can be seen diffuse forms of capillaries and capillary bleeding. In some cases studied, a single thick horizontal S-shaped loop was noted in this field; in other cases there is a fine plexus-like formation of capillaries in a fog-like brownish mass. Outside the border of the capillaries, surrounding the plaque, there can be seen tips of normal vertically arranged capillaries. The lighter field in the lichen planus papule depends on the intracellular edema in the epidermis. The central diffuse

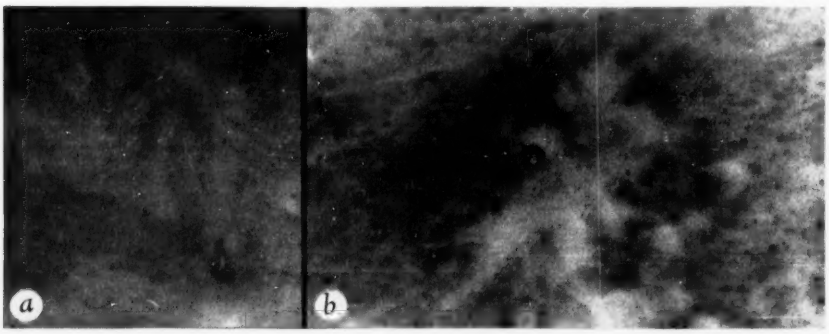

Fig. 4.—The capillary microscopic picture in lichen planus. (*a*) A single papilla. A central bright field surrounded by a border of hairpin-shaped slender capillary loops. (*b*) A plaque.

darker mass in the light area is supposed to represent the degenerative changes of the dermis which take place in older plaques and produce the "falling down" of the epidermis. As the capillary microscopic pictures in lichen planus are uniform and compatible to each other, it seems that the differential diagnosis of lichen planus on the basis of capillary microscopy should not be difficult.

Lupus Erythematosus.—The capillary microscopic picture of lupus erythematosus in the discoid form is definite and characteristic. The picture is much changed from the normal configuration of the skin (Fig. 5*a*, *b*, and *c*). Dominating the picture are round or oval grayish formations which are darker than the surroundings. These represent the keratotic plugs. Surrounding these and also scattered over the fields, the blood vessels appear as thick, clumsy loops running in horizontal and oblique directions. No normal capillaries are visible. The picture varies depending on the status of the disease, since in cases of recent onset the vessels dominate the picture in rete-like formation, surrounding the smaller keratotic plugs (Fig. 5*a*). In older cases, the larger keratotic plugs, irregularly arranged, dominate the picture, while the vessels are more in the background. In lupus erythematosus disseminatus acutus

or subacutus, in some plaques, multiple keratotic plugs surrounded by loops of fine vessels have been found, but there also have been seen some scattered dilated capillary loops of about normal shape surrounding the keratotic plugs. In some cases the vessels protrude from the depths up in a vertical direction and then spread out in a horizontal direction surrounding the plaques. In lupus erythematosus acutus one usually finds the described picture in plaques on the face; but in the generalized lesions the picture appears to be not specific. In the nail folds (Fig. 5*d*) the uneven

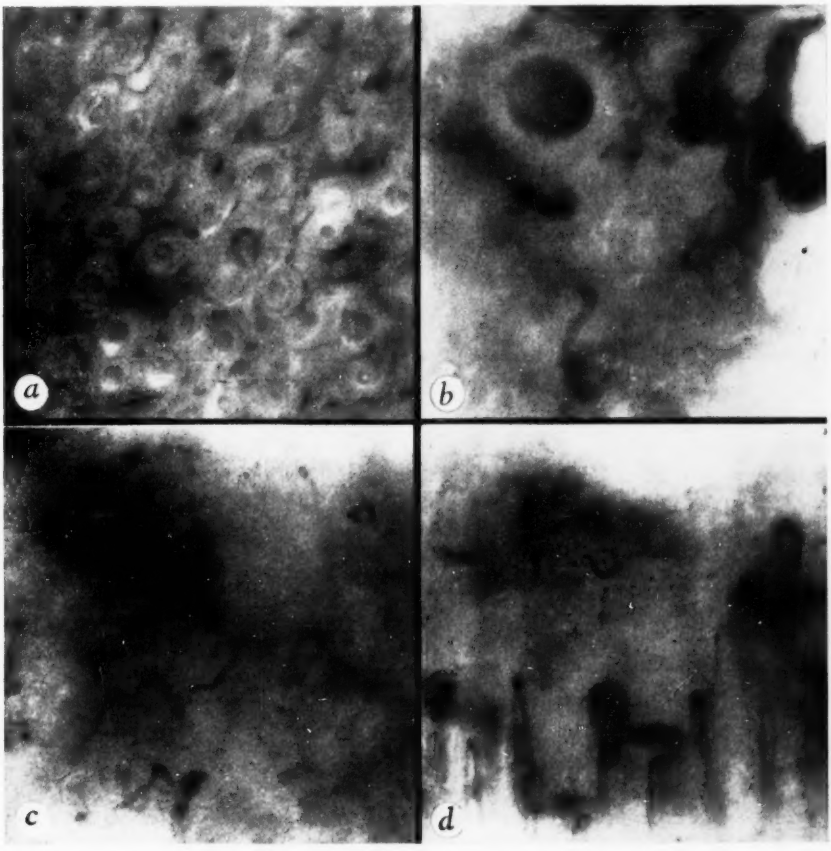

Fig. 5.—The capillary microscopic picture in lupus erythematosus. (*a*) A newer plaque. Arcs of vessels surround the keratotic plugs. (*b*) An older plaque in an acute phase. (Higher magnification.) One keratotic plug. Thick, clumsy loops of vessels. (*c*) A newer plaque in palm of hand in a case of lupus erythematosus disseminatus. (*d*) Nail-fold capillaries in a case of lupus erythematosus disseminatus.

border of the capillaries may be seen. The capillaries are highly dilated both in the arterial and in the venous limbs and in the crests, and the slow granular blood stream is observable. Sometimes the capillary has a corkscrew form. A plaque in the palm (Fig. 5*c*) showed that the capillary changes were similar to those noted in the nail folds.

McCreight and Montgomery,[16] in discussing the vascular changes in lupus erythematosus, stated:

> The earliest changes to occur within the cutis are those of dilatation of the superficial capillaries and lymphatic vessels. . . . Hyperkeratosis without parakeratosis was nearly a constant finding, as was also keratotic plugging, either follicular or extrafollicular. . . . It is apparent . . . that there is no single pathologic change which will allow a definite diagnosis of lupus erythematosus. However, a combination of observations when considered together seems to be relatively specific.

Further, the same authors emphasize that it is impossible for one to distinguish the various types of lupus erythematosus histologically, since the microscopic appearance depends more on the age of the individual lesions than on the type of disease. This agrees with the findings in capillary microscopy. The numerous vessels observed in the acute cases of lupus erythematosus coincide with the findings of Huff, Taylor, and Keys,[17] who reported that the relative temperature of the lesions is higher than the average normal temperature, and that the more active lesions tend to have a higher relative temperature (cf., skin-temperature measurement).[10] The same authors [17] suggested that "chronic discoid lupus erythematosus may be a generalized vascular disease," a possibility which also has been emphasized by Brunsting.[18] The capillary microscopic examination shows that the changes that occur in the blood vessels of the skin in the discoid form of lupus erythematosus are among the first pathologic alterations seen in the skin in this disease. It is not difficult to make the diagnosis of discoid lupus erythematosus on the basis of the capillary microscopy.

Scleroderma and Acrosclerosis.—The dominating feature in generalized scleroderma is the rete-like formation of the pigmentation with the lighter round or oval spots which represent the tips of the papillae (Fig. 6*a*). In some, the tips or crests of the undilated capillaries are visible.

In acrosclerosis the capillary microscopic picture of the skin is similar to that of scleroderma (Fig. 6*b*), but examination of the nail fold of these two diseases reveals some distinct differences. In generalized scleroderma (without Raynaud's phenomenon) the nail-fold capillaries appear normal (Fig. 6*c*), while in acrosclerosis definite pathologic features may be observed (Fig. 6*d*). In acrosclerosis the outer border of the capillaries is regular, while those behind this first row of capillaries are arranged in more irregular lines, as in steps, the one behind and higher than the one in front. Not only do the capillaries vary much in size and shape, but most of them are dilated. The crest is wide, but not curled, and there is tortuosity in a few of them. In cases with necrotic ulcers of the finger, the capillaries seem to be fewer and thinner in the nail fold, and they look as if they were pushed back from the margin. The blood stream in the highly dilated capillaries is slowed, granular (sludged), and, in most of the cases, white corpuscles are seen as white spots in the blood column. The blood circulation is slow, sometimes so slow that it looks as though it would stop.

16. McCreight, W. G., and Montgomery, H.: Cutaneous Changes in Lupus Erythematosus: Histologic Aspects, With Special Reference to Vascular Changes, Arch. Dermat. & Syph. **61**:1-11 (Jan.) 1950.

17. Huff, S. E.; Taylor, H. L., and Keys, A.: Observations on the Peripheral Blood Flow in Chronic Lupus Erythematosus, J. Invest. Dermat. **14**:21-36 (Jan.) 1950.

18. Brunsting, L. A.: Symposium on Diseases of the Skin: Acute Disseminated Lupus Erythematosus, M. Clin. North America **35**:399-409 (March) 1951.

The histopathologic changes in the skin of patients who have acrosclerosis are similar to those of diffuse scleroderma, and we could not recognize any difference in the appearance of the skin between acrosclerosis and generalized scleroderma. In the pictures of scleroderma and acrosclerosis (Fig. 6*a* and *b*) one gets the impression of the increase of pigment and also of the arrangement of the pigment.

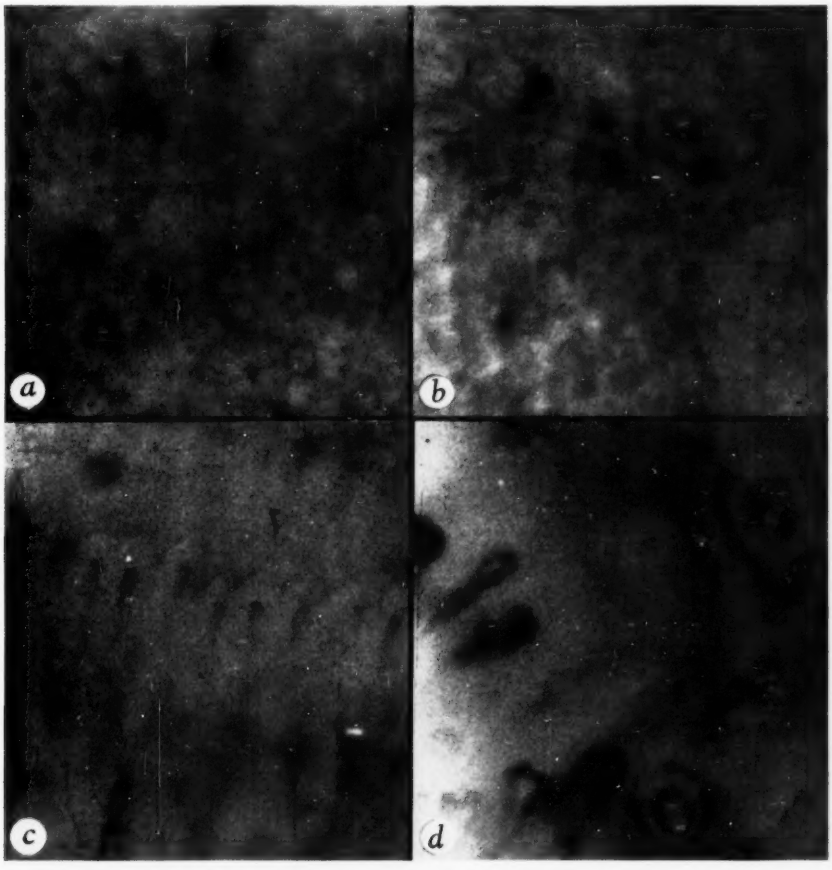

Fig. 6.—(*a*) Scleroderma. Diffuse lesion on back of forearm. Note the capillaries in the center of the light papillae and the hyperpigmentation around the papillae. (*b*) Acrosclerosis. Back of forearm. Compare with *a*, *c*. Nail-fold capillaries in a case of scleroderma. Capillaries about normal. (*d*) Nail-fold capillaries in acrosclerosis. (Higher magnification than *c*.)

CONCLUSIONS

It is our belief that capillary microscopic examination will give additional diagnostic information in the study of skin diseases and will open a door for new possibilities in investigative dermatology. This examination permits helping in a differential diagnosis in certain diseases in a rapid painless way.

The capillary microscope is a necessary part of the dermatologic armamentarium.

USE OF CHEMOSURGERY IN DERMATOLOGICAL PRACTICE

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CHEMOSURGERY is a term coined by Mohs and applied to an original method for the microscopically controlled removal of cancer. Preliminary work was begun by him in 1932 after an observation that zinc chloride injected into tissues chemically killed tissues yet preserved their histologic structures. From 1932 to 1936 the procedure was used in eliminating accessible cancer in mice.[1] Since 1936 Mohs has successfully used his technique in the eradication of skin cancer in humans, with results superior to those reported by any other method of destruction.[2] Inasmuch as with two exceptions the cases in which there has been treatment by us have been limited to cancer of the face, a review of Mohs's cure rate in skin cancer of the face is given. In 174 cases of basal-cell cancer followed for three years 100% cure was shown. Over 30% of these were recurrent. In 94 such cases followed for five years a 100% cure was shown. In 61 cases of squamous-cell cancer without metastasis a 96.7% three-year cure resulted. Many of these were recurrent or otherwise advanced cases.[3]

Mohs's cure rate is 93.6%[4] in a consecutive series of 814 cases of skin cancer on various parts of the body observed for three or more years. No one reporting a similar series of cases has equaled this. Magnussen, of Radiumhemmet of Stockholm, Sweden, using x-ray, radium, electrosurgery, and surgery, reported 88% cure in a similar series. This approaches Mohs's record most closely.[5]

The essential steps in Mohs's technique are as follows:

The patient is first seated in a chair or is allowed to lie on an operating table, whichever presents the operative site most comfortably to the patient and operator

Read at the Seventy-Second Annual Meeting of the American Dermatological Association, Inc., Colorado Springs, Colo., April 26, 1952.

1. Mohs, F. E., and Guyer, M. F.: Pre-Excisional Fixation of Tissues in the Treatment of Cancer in Rats, Cancer Res. **1**:49-51 (Jan.) 1941.

2. Mohs, F. E.: Chemosurgery: A Microscopically Controlled Method of Cancer Excision, Arch. Surg. **42**:279-295 (Feb.) 1941.

3. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Face: Microscopically Controlled Method of Excision, Arch. Dermat. & Syph. **56**:143-156 (Aug.) 1947.

4. Mohs, F. E.: The Effect of the Microscopically Controlled Technique of Chemosurgery on the Prognosis in External Cancer, J. Insur. Med. **5**:16-18 (Jan.) 1950.

5. Magnussen, A. H. W.: Skin Cancer: A Clinical Study with Special Reference to Radium Treatment, Acta radiol., Supp. 22, pp. 1-287, 1935.

alike. Dichloroacetic acid is applied to any keratin overlying the mass to be removed until complete blanching occurs. Keratin not so treated resists the penetration of the zinc chloride fixative and would unnecessarily prolong the procedure. This procedure is followed by the application of a thin layer of zinc chloride paste containing 34.5 cc. zinc chloride saturated (4 : 1) solution, 40 gm. stibnite (80-mesh screen), and 10 gm. sanguinaria. The zinc chloride paste is designed to release zinc chloride to the tissue. The degree of penetration obtained is proportional to the thickness of the layer of paste applied and the time it is allowed to remain in place. A layer about 1 mm. thick is usually employed, carefully applied to the surface of the lesion. To keep the paste strictly in place during the period of fixation it is covered by a thin layer of cotton cut to the pattern of the lesion. All is then covered by an occlusive petrolatum and cotton dressing to prevent it drying out overnight.

The patient is then given a prescription for an analgesic such as acetylsalicylic acid (Aspirin) or Empirin Compound (contains acetylsalicylic acid, acetophenetidin, and caffeine) with codeine, ½ grain (0.03 gm.), to be taken as necessary for pain and directed to return the following day.

When the patient returns, usually 24 hours later, the dressing is removed, along with the remains of the fixative paste. Then by sharp knife the fixed layer is excised in horizontal sections roughly a square centimeter in size—a size convenient both for the technician to cut, mount, and stain and the operator to study microscopically. The excision is just within the fixed tissue, no live tissue being included in the specimen. This makes it ideally a painless and bloodless procedure. If bleeding is accidentally encountered a small piece of gauze impregnated with zinc chloride paste is applied to the spot. This usually controls the bleeding, and sections may be removed from another part of the lesion until the bleeding has stopped completely. This prevents unnecessary delay. Occasionally both the impregnated gauze and pressure with a cotton-tipped applicator are needed to control hemorrhage.

To enable complete orientation of the excised pieces to the involved area throughout cutting, staining, and microscopic examination, the following procedure is carried out: First, an outline of the entire lesion is mapped on paper. It is made about twice the size of the actual lesion in order to facilitate the subsequent necessary markings and symbols to be drawn in. Then, as each piece of tissue is excised it is numbered consecutively, and its edges are dyed with blue and red stains. The number is transferred to the map, and symbols indicating the colored edges are marked on the map. The exact location of the excised tissue is marked with a colored dye on the operative site. Thus, the shape of the piece excised and its colored edges are oriented to the actual operative site.

After cutting, dyeing, and mapping, the pieces are turned over to the technician, who mounts each piece horizontally, bottom side up, on the stage of a freezing microtome. Sections are cut from the undersurface until the first sections covering the entire area of the excised tissue are obtained. These are mounted on a microscopic slide and stained with Mohs's modification of hematoxylin and eosin.[6] The slide is labeled with the patient's name, the number of the piece of tissue, and the date.

6. Mohs, F. E.: The Preparation of Frozen Sections for Use in the Chemosurgical Technique for the Microscopically Controlled Excision of Cancer, J. Lab. & Clin. Med. **33**:392-396 (March) 1948.

As the dye markings are evident microscopically, any cancer seen can be accurately located on the drawn, symboled map. The map, in turn, is oriented with the excised area on the patient. This enables pinpointing of the remaining active sites. The zinc chloride paste is then reapplied to the active sites only. The procedure is repeated daily until the whole area is microscopically cancer-free.

Once the area is cancer-free, sterile petrolatum gauze dressings are applied and changed every 24 to 48 hours for 4 to 12 days while the slough of the residual fixed tissue occurs. The amount of tissue sloughed is approximately 1 to 2 mm. thick. The amount of normal tissue sacrificed is therefore minimal. Removal of the slough, as it occurs, with sterile scissors at the time of changing the petrolatum dressings shortens the period of granulation and healing. Once a clean granulating surface is exposed, 5% scarlet red gauze dressings are used in place of sterile petrolatum gauze, to stimulate granulation and quicker epithelization.

It is well recognized that there are certain types of skin cancer and certain locations on the face in which, the rate of recurrence after conventional measures of destruction, such as surgery, electrosurgery, or x-ray, is too high. The cicatrizing type of basal-cell cancer, lesions about the nasolabial folds, temples, eyelids, and recurrent lesions at any site come readily to mind. In the winter of 1950 to 1951 we had several such cases of recurrence which were an expression of our own failure after the use of such conventional techniques of destruction.

The impression of our group up until that time had been that, although the method as outlined by Mohs in the treatment of skin cancers was logical and his results impressive, it was impractical for routine use in an active dermatological office.

Impressed by such failures and in search of a better procedure, we reexamined our attitude as to the practicability of Mohs's method. One of us (R. R. A.) then spent three weeks with Dr. Mohs in the spring of 1951 learning his technique. All of us in the office have used it since in the treatment of selected cases.

Early in our use of Mohs's method it occurred to one of us (R. R. A.) that the time element could be materially reduced in some cases by using the conventional dermatological technique of thorough curettage of the gross lesion before the zinc chloride paste was first applied. It seemed that by this slight modification of the technique from one to several days might be saved, depending on the size and thickness of the lesion, while none of the advantages would be sacrificed. We believe that this combined technique has proved both practical and advantageous in our hands. The object of this paper is to give the experience we have had in our office with the use of Mohs's method of treatment of skin cancer using, however, this slight, but we think important, modification in technique.

Fourteen of the 30 cases of basal- and mixed-cell cancers treated by us with chemosurgery were recurrences (46.6%). All but two such recurrences developed after original curettage and desiccation.

Chemosurgery has a number of advantages: 1. It offers a microscopically controlled means for the removal of malignant skin growths. Although technical errors or misinterpretation of the microscopic picture may confuse those with limited experience, the procedure appears to afford a greater assurance of the successful removal of the cancer than is had when the more conventional methods of removal have been used. 2. The eradication of cancer is obtained with a minimum amount of destruc-

tion of normal tissue. Probably less normal tissue is destroyed by paste than by electrodesiccation after curettage. 3. It is an ambulatory method of treatment, and thus may be an office procedure.

This method also has some disadvantages: 1. A laboratory equipped with a microtome and materials to cut, stain, and mount tissue sections must be at hand, preferably as a part of the office equipment. 2. A technician who is especially trained to carry out this part of the procedure must be available. The operator must be familiar with and trained to interpret both vertical and horizontal sections of the histopathology present. A knowledge of cytology is very important, for the operator must be able to follow strands of tissue to their ends, differentiating cancer from sebaceous, sweat, and mucous glands, thrombosed blood vessels, and from cellular infiltrate resulting from tissue reaction to the chemical. 4. There is some pain or discomfort to the patient. A number of patients needed no analgesic. The majority of those who did found that acetylsalicylic acid controlled the pain. A few needed Empirin Compound with codeine, ½ grain (0.03 gm.). 5. Daily visits to the office are necessary until the examined tissue is cancer-free. 6. The steps in the procedure are exact and must be carefully and systematically carried out. This is hard work and time-consuming.

Probably the main question as to the utilization of the method as a routine office procedure relates to the matter of time. How long does it take? That depends largely on the location and the size of the lesion. Fixed tissue is easier to dissect than is mobile tissue. A lesion on the eyelid or in the nasolabial fold is more difficult and therefore takes longer to dissect than one on the level contour of the flush area of the cheek. Also, obviously, the more tissue there is to be dissected the longer it takes. In the main, the operator's time is consumed in two procedures: 1. The surgical removal of the fixed tissue. The time for this has varied from 5 to 45 minutes for the first dissection, at which time the entire fixed tissue has to be removed. Usually, at each succeeding day there is less tissue to be excised and, therefore, less of the operator's time is consumed. 2. The microscopic examination. The time necessary for the microscopic examination of the stained specimen depends on the number of specimens to be studied. Usually, about five minutes is consumed with each specimen. The total time depends on the number of microscopic slides studied.

With practice in these procedures our technique has improved. This has resulted in a steadily increasing saving of time.

OBSERVATIONS

1. Of the total of 36 cases of cancer in which there was treatment with chemosurgery the gross lesions in 22 cases were initially curetted before the zinc chloride paste was applied. In 10 of these 22 cases in which there was such treatment no cancer was seen in the first specimen of fixed tissue examined. In these 10 cases our modification of the technique permitted the completion of the operation in 24 hours.

2. Four of our cases illustrate the common observation that some additional procedure other than the conventional ones is needed in the successful management of occasional cases of skin cancer. In one case of morphea type of basal-cell cancer

included in our series of selected cases pseudopods of malignant tissue could be grossly observed. In three other cases, the curette when used dropped into one or several pockets of cancerous tissue. Before arriving at cancer-free tissue in such cases an area several times the diameter and expected depth of the observed gross lesion was necessarily destroyed.

3. In two cases in which there had been much previous treatment by x-ray the application of zinc chloride paste resulted in more extensive sloughing than had been observed in comparative cases in which x-ray had not been used. This observation had been previously emphasized by Mohs.

4. In the morphea type of basal-cell cancer and in some lesions where the scar is predominant little advantage is gained by initial curettage. In such cases Mohs's technique without modification may be more satisfactory.

5. Of the 22 cases in which curettage was used an average of two daily visits was necessary for the completion of the destruction of the lesion as compared with five daily visits for the 14 cases in which curettage was not used. Thus, an average of three days was saved by the operator and patient. Although we do not have enough cases to make this comparison statistically significant, the observation has been consistent. We think that it is a logical consequence of the technique and expect to see it continue.

6. After the second or third day of application of the zinc chloride paste a cellular infiltrate appears in the corium which becomes more dense each succeeding day. This reaction to the chemical when severe tends to mask the microscopic picture and thus makes it more difficult to recognize cancerous tissue. The initial curettage in most cases results in cancer-free tissue before this infiltrate has had time to appear in annoying amounts.

7. Daily visits to the office would have been necessary in order to know the exact day of healing. We thus have no exact data for definite statements of time of healing. However, the rapidity of healing of the cancer-free tissue with the method of dressing and débridement of the wound carried out by Mohs and followed by us has been impressive. Our opinion is that it compares more than favorably with similar results occurring after electrosurgery.

8. After having used the method of chemosurgery in the treatment of 36 selected cases of skin cancer the opinion of our group is that the greater assurance of successful removal of the cancer more than compensates for the time and hard work expended in the removal.

COMMENT

This paper is a preliminary report of our experience in treatment of skin cancer in our office using a modification of Dr. Mohs's procedure of chemosurgery with microscopic control.

The curettage of the gross lesion before the initial use of the zinc chloride paste has, in our experience, materially reduced in most cases the number of days the patient has to be seen. This has helped to make the procedure practically useful in the treatment of skin cancer in an active dermatological office.

Mohs has spent years perfecting his method and his technique. Whether we, after a relatively short apprenticeship under him, can obtain results comparable with

his is still a question. Likewise, the value of our modification of his technique remains to be substantiated statistically. We believe that we are applying it successfully, and that others can do the same. The validity of this assumption will be verified or refuted only by the passage of time.

ABSTRACT OF DISCUSSION

Dr. Harry R. Foerster, Milwaukee: Dr. Lunsford and his associates have accurately appraised and evaluated a logical and scientific adaptation of the oldest method of cancer therapy, chemical destruction. They are to be commended on their initiative in applying Mohs's surgical procedure to dermatological practice and on developing a practical modification of his technique to facilitate office treatment. They have thus enlarged the scope of dermatologic treatment in a field in which the dermatologist has been losing prestige by encroachment of other specialties.

Mohs's treatment of advanced skin cancer is distinctly a surgical and hospital procedure that, in his hands, has produced remarkable results with which you are all no doubt familiar.

In reviewing Mohs's work with him recently I observed the facility and efficiency with which small epitheliomas, nevi, and borderline lesions can be treated by this method as an out-patient procedure and by the excellent cosmetic end-results he has obtained. I was impressed by the need of specialized training in both the surgical technique and the preparation and interpretation of the histologic specimens. The correlation of these various steps is the basis of successful treatment and indicates its superiority over other methods in properly selected cases. There is also an undeniable advantage in having one person do both the surgery and the histologic study at the same time, provided he is proficient in both. He can visualize the microscopic picture at a given site and immediately attack the lesion accurately. This method is time-consuming as well as exact. It is not a practical method of treating epitheliomas for the dermatologist without sufficient material to keep up his technique, nor without the volume of work or means to justify employing a specially trained technician, which is a necessity.

Chemosurgery of epitheliomas is a special field adaptable to dermatologic practice chiefly for adequately staffed groups, especially when affiliated with clinics or hospitals and where a surgically trained dermatologist can devote the necessary time to it.

The diagnosis and treatment of skin cancer belongs primarily in the field of dermatology. The dermatologist is best equipped by training and experience to recognize and correctly diagnose clinically early epitheliomas and to differentiate other lesions. He should also be best equipped to determine intelligently the choice of treatment in an individual case among the many effective and approved methods now available. There are many cases in which an accurate diagnosis can be made without the need of biopsy and in which there can be effective treatment by the dermatologist without resort to any type of surgical procedure. It is possible that chemosurgery may replace direct excision and plastic surgery in those cases in which nonsurgical methods such as radium, x-ray, and electrodesiccation treatment are inadvisable. It will undoubtedly also replace these latter methods in many dermatologic cases in which they are now employed.

The highest percentage of cures and the lowest percentage of recurrences in the treatment of skin cancer will be obtained where the choice of therapeutic procedures is widest and can be determined by the needs in the individual cases rather than by the limitations of the physician or his facilities. The Mohs method as modified by Lunsford and his associates, is, therefore, one with which we should thoroughly familiarize ourselves, particularly if we are engaged in teaching and training future dermatologists. This method, for the excellent exposition of which we are indebted to the presenters, is a very definite contribution to our armamentarium.

Dr. E. A. Oliver, Chicago: As I said in my presidential address, I believe that in 95% of the cases of skin cancer there can be adequate treatment by the dermatologist. There are, however, a certain number of recalcitrant lesions that can be, and should be, treated by the Mohs technique. I have been a patient of Dr. Mohs and have seen much of his work. I have been to him on four different occasions for treatment of my own lesions, and I have the highest admiration for his work, his patience, and his perseverance.

I am glad to know that Lunsford and his associates are using this treatment. It is a splendid method of treating certain types of lesions, but, in my opinion, it is not a treatment for the average case of ordinary epithelioma. It is a valuable method for severe, recalcitrant lesions, particularly those around the cartilage of the nose, the ear, and on the forehead, especially when cartilage or bone has been involved. It is also of great value in those cases in which there has been resistance to x-ray or radium therapy. I have referred about eight patients to Dr. Mohs in the last year or two, and he has had splendid results with all of them.

This is a painstaking, very careful method of treatment, and it cannot ordinarily be done in an office unless the physician has several trained technicians working with him and a man who knows histopathology. It is not a painless method. Depending upon the location of the lesion, one is apt to suffer considerable pain of a toothache-like nature an hour or two after the application of the zinc chloride mixture for the rest of the afternoon and night. When the dead tissue is excised, of course, there is no pain.

In my opinion, chemosurgery is better treatment than plastic surgery, because with his technique Dr. Mohs is able to track down the epitheliomatous growth until he is absolutely certain that there are no more cancer cells present, and in view of the fact that basal-cell epitheliomas sometimes spread in a fan-like manner, this to me seems an ideal method for intractable cases.

Dr. Richard L. Sutton Jr., Kansas City, Mo.: I think that I should preface my remarks by arguing against myself at the start. I have not visited Dr. Mohs. I have not observed his work. I have the greatest respect for the men of our society who commend it. I am sure that Dr. Mohs has obtained cure in cases that I do not consider myself competent to tackle. However, these ideas occur to me in criticism: 1. The description of the tissue removed as "pinpointing the lesion." A bit of tissue a centimeter across is not a pinpoint. A section through such a mass of tissue could even miss cancer within it.

2. Microscopic control. In my experience it seldom requires a microscope to show whether the tissue is cancer-free. When one removes the whole tumor, along with a margin of normal tissue, and makes a gross section across it, possibly in several directions, perhaps with two or three diameters magnification, then familiarity with gross sections can satisfy one fairly well as to whether one has got beyond the edge or not.

3. Minimal sacrifice of tissue. I can use an electric cautery in such a fashion as to sacrifice extremely little tissue other than that which I desire sacrificed, including the operation of peeling basal-cell tumors off eyelid skin. Furthermore, it is only occasionally that one is deeply concerned with minimal sacrifice. One is usually concerned primarily with successful amputation of the growth and secondarily with cosmetic results.

4. Minimal pain of the wound. The electric cautery excision wound is painless, unless it becomes infected. Yet I would admit that pain is not a consideration of great importance in the cure of cancer. The objective is to obtain the cure.

This objective is, basically, amputation of the growth. I believe that it is fundamentally erroneous to start in the center of a tumor and to chase it peripherally. I think that correctly one should intend to envelop it (as in a military operation aimed at destruction of each individual enemy) and should achieve his amputation procedure, by whatever tool he chooses, by cutting beyond the edge insofar as he is capable of determining the edge by preliminary palpation, observation, etc. Of course, each man is expert with his own tools. I have often said to medical students that it is quite possible to cure a moderately extensive growth on a man's nose with a brick. But you could not do so elegantly.

Finally, as regards Dr. Mohs's having spent years perfecting his technique—well, there aren't any very young men here, and many of us have spent quite a number of years perfecting our techniques.

I hope, indeed, that it is not stubbornness that makes me so skeptical.

Dr. Marion B. Sulzberger, New York: I am sure that I voice the thanks of all of us in expressing our gratitude to the presenters of this very interesting report. I am sure also that I voice the consensus when I say that, just as Dr. Lunsford stated, only time will tell whether

the modification of the Mohs method which the authors have introduced will prove valuable, and whether this method is really practical as an office procedure. In considering the Mohs method in relation to Dr. Ronchese's report, I should like to ask whether anyone here knows if Ronchese's described red fluorescence in prickle carcinoma can be observed in prickle-cell epitheliomas after the fixation of the tissue by the zinc chloride of the Mohs method. If so, it might prove to be time-saving and of practical help to look for the points of red fluorescence in the fixed tissue during the procedure of chemosurgical ablation of prickle-cell epitheliomas.

Dr. Norman N. Epstein, San Francisco: The Mohs technique of chemosurgery has a definite place in the treatment of skin cancer and is to be preferred for certain lesions which are not readily accessible. It is also to be preferred in lesions where it is essential to conserve as much of the surrounding tissue as possible.

It was first applied in the University of California visible tumor clinic to lesions which neither the surgeon nor the radiologist nor the dermatologist were willing to treat. Patients with such lesions were sent to Dr. Mohs for treatment. Since that time Dr. Gilbert Bierne has been trained in the technique, and he is given selected cases to do.

I agree with the other discussers that skin cancer, its diagnosis and treatment, is essentially a dermatological problem. Dermatological methods, including radiation, are effective and satisfactory for the large majority of these lesions. However, in a small percentage of selected cases surgical excision followed by a graft or chemosurgery are the methods of choice.

Dr. Paul E. Bechet, Elizabeth, N. J.: The authors should be congratulated on their clear exposition of the Mohs technique and its results in the treatment of carcinomata of the skin. Chemotherapy of skin cancer is a venerable subject and was first used by Rousselot, chiropodist to the Dauphin of France. As early as 1769, he published the results of several years of experience with arsenical pastes in the treatment of skin cancer. His favorite formula consisted of cinnabar, sanguinaria, and arsenic, this being mixed in the palm of the hand, saliva being used as a diluent; the paste was then applied to the cancer and kept in place with spider web. Twenty years later Friar Come and his pupil Friar Bernard used a formula consisting of 0.32 gm. powdered arsenic, 1.62 gm. cinnabar, and powdered burnt shoe soles, a pinch, which proved highly successful in the treatment of cutaneous cancer. They purchased this formula from a barber surgeon for 3,000 livres. In 1874 Alexander Marsden presented in book form the results from the use of his famous paste in carcinotherapy after an experience with it for 17 years. The formula consisted of 7.7 gm. arsenious acid, and 31.1 gm. acacia mucilage. Marsden's excellent results gave a great impetus to the method, and it was still used occasionally at the turn of the 20th century, when it fell into the hands of quacks. Samuel Sherwell introduced in 1887 his highly successful use of chemotherapy by the application of acid nitrate of mercury, after thorough curettage. I can personally attest to the excellency of both cosmetic and therapeutic results. So the method is not new, and it has had many variations.

Dr. Herman V. Allington, Oakland, Calif.: We wish to thank all the discussers.

We agree that special training is needed and believe that the three weeks which one of us (R.R.A.) spent with Dr. Mohs is probably the minimum of time required to become familiar with the technique. We also agree that it would be impractical to operate without a technician trained and capable of doing the routine laboratory work entailed in preparing the sections for microscopic examination. Our technician also does other routine laboratory work and is a valuable full-time employee. I believe Dr. Eckblad trained a secretary to prepare his sections. I should think that intelligence, dexterity, and integrity are more important than previous laboratory training, and that the problem of a technician would not be insurmountable in most offices.

Thus far we have used this method for the most part in selected cases. It is not, however, a tedious procedure when applied to the average small epithelioma, and we find that we are using it more and more routinely as we become more experienced in its use. However, we feel that the effort and the expense of equipment would be worth while to us even if we only used it in the occasional case in which its advantages are most needed.

We know that the method is not painless. However, we frequently have patients who do not bother to obtain the analgesic which we always prescribe. In most cases the major discomfort occurs within a few hours after the application of the paste. None of the patients with whom we have started treatment have thus far failed to complete treatment.

We have thus far not had trouble with the problem of secondary infection mentioned by Dr. Oliver. We attempt to make it a sterile procedure, but we realize that secondary infection is always a threat and should be kept constantly in mind.

With respect to Dr. Sutton's discussion, we should like to emphasize that we cannot always determine either by observation or by curettage the limits of an epithelioma. By the technique of mapping and marking the wound as the tissue is taken for microscopic study and by dyeing the margins of the individual sections it is possible with the aid of the microscope to localize any residual cancer with considerable accuracy. We feel that this is the major advantage of the method. It enables one to follow areas of residual cancer in whatever direction they may extend until the growth is eliminated.

I do not know, Dr. Sulzberger, of anyone who has yet applied the filtered ultraviolet-light technique to this problem.

As Dr. Bechet stated, this is an extension and refinement of the old "cancer paste" treatment. Those who deplore it on that ground, however, fail to appreciate the important difference, namely, that of microscopic control.

ARTHROPODS OF DERMATOLOGICAL INTEREST

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THE IMPORTANCE of arthropods as possible transmitters of pathogenic organisms is well known in general medicine.[1] The dermatologist occasionally sees a patient suffering from a systemic disease with cutaneous manifestations in which an arthropod has served as a vector of the disease. However, he sees far more patients with cutaneous diseases in which an arthropod is the etiological agent.

The dermatologist is expected to have a knowledge of the symptomatology of these diseases and in general can arrive at a diagnosis as to the nature of the dermatosis. In many of the dermatoses due to the arthropods he may not be able to determine the causative parasite by mere inspection, but the general pattern of the eruption may be sufficient to give him a clue as to the nature of the agent.

We feel that the dermatologist who deals with these various conditions should have at least an elementary knowledge of the parasites involved. In order to facilitate the study of these arthropods, we are presenting a concise summary of those of importance to the dermatologist. They are classed according to modern entomologic concepts so as to show their relationship to one another. Essential morphologic features are indicated, as well as the dermatoses produced and the diseases transmitted (with the etiologic agent shown), for the individual groups of arthropods. Representative species, especially those common in the United States, are named where possible, and common and colloquial names are also shown both for organisms and diseases.

PHYLUM ARTHROPODA

Phylum Arthropoda is the largest of the animal phyla and the most highly evolved of all the invertebrate groups. Arthropods are invertebrate, many-celled, segmented, bilaterally symmetrical animals, having paired articulated appendages and an exoskeleton composed of chitinous secretions. There is always a complete digestive tract, a blood system, and a central nervous system. Many arthropods

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have become land or air forms, and the gills have been sunk into the body to form book-lungs or have been replaced by tracheal respiration. During growth the external skeleton is periodically molted in its entirety.

The sexes are separate, and postembryonic development usually involves some degree of metamorphosis. The stages in development consist in egg, one or more larval stages resembling the adult, and adult. In several insect groups the last larval stage and the adult stage show marked morphological differences, with a pupa or "resting stage" interposed between these two.

The arthropod, as a disease-producing organism, may either invade the tissues of the host, introduce toxins on or into the skin, produce a state of hypersensitivity with resulting allergic manifestations, or traumatize the skin with resulting dermatoses and pyogenic infections.

Although there are about 13 classes in the phylum, only the following four classes contain species of interest to the dermatologist: Crustacea, Chilopoda, Arachnida, and Hexapoda.

Class Crustacea (Crabs, Crayfish, Lobsters)

All the arthropods in the class Crustacea are aquatic or semiaquatic and breathe by means of blood gills. They do not directly cause diseases of dermatological interest, but various Cyclops species of the order Copepoda (water fleas) transmit Dracunculus medinensis (the guinea worm), causing dracunculosis, and Gnathostoma spinigerum (the cat nematode), causing gnathostomiasis (creeping eruption).

Class Chilopoda (Centipedes)

The arthropods in the class Chilopoda are worm-like, with one pair of legs on each of the numerous fairly similar body segments. They have poison glands opening near the tip of the fangs terminating the first pair of legs. They are almost completely harmless to man, as only a few species have jaws strong enough to break the human skin. Most of the poisonous species are found in the genus Scolopendra, causing centipede venenation, with local but few general symptoms. There are some Scolopendra species common in the southwestern United States.

Class Arachnida (Spiders, Scorpions, Ticks, Mites)

The body of the arthropods in the class Arachnida is usually divided into two regions, the cephalothorax and the abdomen, with no antennae or wings. Adults have four pairs of legs attached to the cephalothorax, whereas larvae have only three pairs of legs.

The class is divided into 9 to 12 orders, with only one order, the Acarina, of real dermatological interest. Two other orders, the Scorpionida and the Araneida, are of importance because of the possession of poison glands.

Order Scorpionida (True Scorpions).—The scorpion has a characteristic form with a long segmented tail-like abdomen ending in a bulbous sac and sting through which venom is discharged. Most scorpions are of little significance, with a sting no worse than that of the bee. The most venomous of the scorpions are in the genus Centruroides, with the following two species, causing scorpion venenation, being the most important: species C. suffusus (the "Durango" scorpion of Mexico) and species C. sculturatus (found in Arizona).

Order Araneida (Spiders).—Spiders differ from all other arachnids by having the abdomen unsegmented and attached to the cephalothorax by a short pedicle. Modified second antennae just above the mouth end in a clawed terminal segment, through the tip of which poison glands discharge. Only a few species are actually dangerous to man. There are no spiders in the northern half of the United States that need to be feared, and only the bite of the Latrodectus in the southern half of the United States is dangerous.

Family Aviculariidae (Tarantulas): These are large, hairy, and fierce-looking, common in the tropics and subtropics, but essentially innocuous.

Family Theridiidae (Black-Widow Group): It contains the most venomous species, found in the genus Latrodectus.

Species L. mactans (black-widow or hourglass spider). This spider is coal-black, with red or yellow markings. The most constant and distinguishing mark is the red hourglass-shaped one on the ventral aspect of the female's abdomen. The bite of the female causes arachnidism (spider poisoning, with violent symptoms but few fatalities), whereas males seldom or never bite, and their poison is not potent when compared with that of the female.

Order Acarina (Ticks and Mites).—The general absence of body segmentation distinguishes ticks and mites from other arachnids as well as from insects. The cephalothorax and abdomen are fused, giving a sac-like appearance. Also, a head is lacking, and wings or antennae are never present. Many species are free-living and predaceous. Large numbers of species are parasitic, being either external parasites feeding on the blood of the host (ticks) or burrowing in the skin of the host (follicle and mange mites). Some species are parasitic in the larval stage (chiggers), but free-living in the adult stage. Still other species (food mites) feed on stored food products. There are eight suborders, but only five contain mites known to be parasitic on man. These mites are distributed among seven superfamilies.

Superfamily Demodicoidea (Follicle Mites): The body is vermiform, much prolonged behind, distinctly annulate or ringed, with rudimentary legs. The mouth parts are fitted for piercing. These mites parasitize the hair follicles and sebaceous glands of mammals. There is one family with a single genus, Demodex.

Species D. folliculorum (human follicle mite). It is believed to be purely non-pathogenic by some authors. Others attribute some cases of rosacea and a condition known as pityriasis folliculorum to this mite.

Superfamily Ixodoidea (Ticks): The large size and leathery integument distinguish ticks from all other mites. Life cycles are variable, some ticks requiring only a single host, whereas others drop from their host after each feeding. All ticks are parasites of vertebrates and are adapted exclusively for blood-sucking. Ticks are divided into two families.

Family Argasidae (Soft-Bodied Ticks): The dorsal shield, or scutum, is absent. There are four genera, of which the genus Ornithodoros is the most important medically because it is a vector of relapsing fever (the agent is Borrelia duttonii) in addition to causing tick bites.

Family Ixodidae (Hard-Bodied Ticks): The scutum, a hard dorsal shield, is small and anteriorly placed in the female, but covers almost the entire dorsal surface in the male. Sculpturing, furrows, and color pattern on the dorsal surface are

characteristic for each species. The great majority of ticks are in this family and have a world-wide distribution. There are some 10 to 12 genera, with only two of medical importance in the United States.

Genus Dermacentor. There are some seven species in North America and none in South America. It is very ornate, with eyes and festoons. Males are without ventral shields. The basis capituli is quadrangular in the dorsal view.

Species D. andersoni (wood tick). The goblets of the spiracular plate are large and not very numerous. It is found in the western United States, with greatest abundance in the northern part of the Rocky Mountain region.

Species D. variabilis (dog tick). The goblets of the spiracular plate are small and very numerous. It is found in North America, east of the Rocky Mountains.

Species D. occidentalis (Pacific Coast tick). This tick is found along the coastal ranges of the Pacific coast of the United States. All three species mentioned above cause tick bites and tick paralysis (except D. occidentalis), and transmit Rocky Mountain spotted fever, the agent being Rickettsia rickettsii, and tularemia, the agent being Pasteurella tularensis.

Genus Amblyomma. This is a large genus of ornate ticks found principally in the tropical and subtropical regions.

Species A. americanum (Lone Star tick). This tick is identified by the solitary white spot on the posterior margin of the scutum of the female. It is widely distributed in many southern states east of central Texas. It causes tick bites and transmits spotted fever (in Texas and Oklahoma) and tularemia.

Superfamily Parasitoidea (Parasitoid Mites): Its structure allies these mites with the ticks. The body often has a leathery shield. There are three large families, but only one is of medical interest. This is the family Dermanyssidae, the members of which are all true parasites of reptiles, birds, and mammals and always have a dorsal shield. There are three important species in this family.

Species Dermanyssus gallinae (chicken mite). The mites will attack persons handling fowl or sleeping near infested areas. It causes gamasoidosis (fowl-mite dermatitis).

Species Allodermanyssus sanguineus (mouse mite). It transmits rickettsialpox. Its agent is Rickettsia akari.

Species Liponyssus bacoti (tropical rat mite). It transmits endemic typhus (potential transmitter). Its agent is Rickettsia mooseri.

Various Dermanyssus species (bird mites). They are parasites of pigeons, sparrows, etc., and may cause a mite dermatitis like the fowl mite.

Superfamily Trombidoidea: Only the family Trombidiidae contains species frequently parasitic in the larval stages on man and animals while the adults are free-living.

Subfamily Trombiculinae (Chiggers, Red Bugs, Harvest Mites): This was previously known as the family Trombiculidae. The adults are free-living, very hirsute, brilliantly red or orange colored. The larvae are eight-legged parasitic blood-suckers, infesting vertebrates exclusively and known as chiggers or harvest mites.

Species Eutrombicula alfreddugesi (common chigger). This species was formerly known as Trombicula irritans and in the older literature as Leptus irritans. It is

the common chigger of North America and is very prevalent in southern states during the summer months. The larval mites are red and minute, and they easily penetrate clothing. It causes trombidiasis (chigger-bite dermatitis).

Species Trombicula akamushi (Japanese red bug). It causes chigger-bite dermatitis and transmits scrub typhus (tsutsugamushi fever). Its agent is Rickettsia orientalis.

Superfamily Tarsonemoidea (Predaceous Mites): These are soft-bodied forms, with the body divided into cephalothorax and abdomen. These mites are primarily plant-inhabiting or infest foods of various kinds. A few species are parasitic, and one may attack man.

Species Pyemotes (Pediculoides) ventricosus (grain-itch mite). This minute mite feeds on the larvae of insects which infest seeds, grains, plants, or their produce. The fertilized female becomes greatly swollen. It causes grain itch. Man is attacked when handling infested material or while sleeping on infested straw.

Superfamily Sarcoptoidea (Itch and Mange Mites): These mites are parasitic in all stages, living out their entire life on their hosts and infesting the skin, tissues, feathers, or hairs. There is no division between cephalothorax and abdomen.

Family Sarcoptidae: The species are all skin-infesting in man and animal.

Genus Sarcoptes. It contains those species that produce true scabies of man and animal. The animal Sarcoptes may infect man but do not live on man, and if the animal contact is removed the Sarcoptes will disappear.

Species S. scabiei (human-itch mite). The mite burrows horizontally in the epidermis, laying eggs as she burrows. These eggs hatch, and the larvae and nymphs in turn form shallow burrows in the skin. It causes scabies (the itch, sarcoptic mange).

Superfamily Tyroglyphoidea (Food Mites): They are never true parasites of man, but are temporarily contracted as a contaminative infestation from handling food products that are infested. They abound in dried fruits and other foodstuffs. These are minute mites with a smooth body surface showing no bossing or ridging.

Species Tyroglyphus longior (cheese mite). It causes copra itch.

Species Tyroglyphus siro (cheese mite). It causes vanillism.

Species Glyciphagus domesticus and species Aleurobius farinae (cereal mite). They cause grocer's itch. It is caused by all the species, in addition to the specialized itch of each species.

Class Hexapoda (Insects)

The class Hexapoda is the largest and most important class of arthropods. The insect has a distinct head, abdomen, and thorax. The head bears mouth parts, eyes when present, and one pair of antennae. The thorax consists of three segments, usually well-marked, with one or two pairs of wings in the adult state typically and three pairs of thoracic appendages, or legs (i. e., hexapods).

There are some 33 orders of insects with the four orders, Anoplura (lice), Hemiptera (true bugs), Siphonaptera (fleas), and Diptera (flies) of most medical importance. The Coleoptera (beetles) and Lepidoptera (moths and butterflies) are of some dermatological interest.

Order Hymenoptera (Ants, Bees, Wasps).—Some insects in this group (bees and wasps) may produce symptoms by poisonous stings.

Order Coleoptera (Beetles).—Beetles typically have two pairs of wings, of which the first pair are greatly thickened to form a protective cover. They are important because of the vesicating effects of some species.

Family Meloidae (Blister Beetles): Beetles of this family contain a volatile vesicating substance, cantharidin, in their body fluids. Accidental crushing of the beetle or rubbing the body fluid on the skin is sufficient to produce the bullous dermatitis. The following are some type species:

Species Cantharis vesicatoria (Spanish fly) and species Epicauta solani (striped blister beetle). They cause bullous dermatitis.

Family Staphylinidae (Rove Beetles): It contains some species with vesicating properties due to a vesicating substance in the body fluids. This substance is not cantharidin.

Genus Paederus. This genus is distributed throughout the world. It is almost the only genus with species having vesicating properties. It causes bullous dermatitis.

Order Lepidoptera (Moths and Butterflies).—It is of interest because of the urticating dermatitis produced by the caterpillar (the larva) of some species. The more important urticating caterpillars in the United States are found in the families Megalopygidae (flannel moths), Lymantriidae (tussock moths), Saturniidae (giant silkworms), and Eucleidae (slug-caterpillar moths). The following are the two most important species:

Species Megalopyge opercularis (puss caterpillar), the most important species in southern United States, and species Euproctis phaeorrhea (brown-tail moth), the most important species in eastern United States. They cause caterpillar dermatitis (urticating dermatitis). The urticating hair may be a simple bristle or a hollowed spine associated with poison-secreting cells. The dermatitis may be due to direct contact with the caterpillar or with wind-blown hairs.

Order Hemiptera (True Bugs).

Suborder Heteroptera.—They have typically two pairs of wings, but some families are wingless. The species of medical importance are blood-sucking forms with only two families of any importance.

Family Cimicidae (Bedbugs): They are reddish-brown, flattened, with an oval contour and, at most, vestigial wings.

Genus Cimex. This is the type genus with only two species invading human habitations. It causes bedbug dermatitis (bedbug bites).

Species C. lectularius (common bedbug).

Species C. hemipterus (tropical or oriental bedbug).

Family Reduviidae (Assassin Bugs): These conenose bugs have well-developed wings, an elongate and ovoidal abdomen, a long narrow head, and a distinct neck. This family is larger than the Cimicidae, with over 3,000 species. The majority feed on the blood of insects, but at least 75 species feed on the blood of mammals, including man. It is important, because some species are vectors of Trypanosoma cruzi, the agent of Chagas' disease, and all are avid blood-suckers, producing painful wounds in some species.

Species Triatoma sanguisuga (Mexican bedbug or conenose). The bite is severe.

Species Panstrongylus megistus (Triatoma megista). This is the most important vector of Trypanosoma cruzi.

Species Reduvius personatus (kissing bug). This is a fierce biter, producing general symptoms.

Order Anoplura (Biting and Sucking Lice).—This order formerly included only sucking lice.

Suborder Mallophaga (Biting Lice).—It is not known to transmit disease, nor is it an important cause of dermatitis.

Suborder Siphunculata (Sucking Lice).—These lice are exclusively ectoparasites of mammals, being blood-suckers.

Family Pediculidae (Human Lice): This is the only family containing parasites of man. All the lice are small, flattened, with a toughened skin and wingless. They are found from the Arctic to the tropics and are not influenced by seasons.

Species Pediculus humanus *var.* capitis (head louse). It is similar to the body louse, but slightly smaller. It confines itself to the hair of the scalp primarily, but can lay eggs on body hair and clothing.

Species Pediculus humanus *var.* corporis (body louse). It is found principally on the body and lays its eggs on clothing, but will also lay eggs on body hairs. The two species cause pediculosis and transmit epidemic typus, the agent being Rickettsia prowazekii, and epidemic relapsing fever, the agent being Borrelia recurrentis.

Species Phthirus pubis (crab louse). It is usually confined to the pubic and perianal region, though it has been reported from all body hairs. It causes phthiriasis (crabs).

Order Siphonaptera (Fleas).—Fleas are wingless, with the body compressed laterally and with an especially long pair of hind legs adapted for jumping; the mouth parts are adapted for piercing and sucking. All fleas are ectoparasites of warm-blooded animals in the adult stage, visiting their hosts primarily for food. There are two medically important families.

Family Hectopsyllidae

Species Tunga penetrans (jigger, sand flea, or chigoe).The only important flea in the family and the smallest flea known. It is found in Florida and in subtropical and tropical America. It causes Chigoe infestation.

Family Pulicidae

Species Pulex irritans (human flea). Man is the primary host. It is found all over the earth.

Species Ctenocephalides canis (dog flea) and species Ctenocephalides felis (cat flea). These two species are the common ones found in the house and readily bite man. They cause flea dermatitis.

Species Xenopsylla cheopis (tropical rat flea). It is essentially a flea of warm climates, but it is found on the coasts of the United States. It is a rat parasite, but attacks man. It causes flea dermatitis and transmits bubonic plague, the agent being Pasteurella pestis, and endemic typhus, the agent being Rickettsia mooseri.

Order Diptera (Flies).—Flies are typically equipped in the adult stage with a single pair of membranous wings. Adults are mainly diurnal, feeding on nectar, exudates from plant and animal wounds, or decaying animal or vegetable matter. Some flies have acquired the blood-sucking habit. The larvae may be scavengers, parasites on man and animals, or parasites on other insects.

Flies may act as mechanical or biological vectors of disease organisms, may produce myiasis, or may act as intermediate hosts of helminths. They may be classified as blood-sucking, with this grouping cutting through families and sexes within species, or filth flies, not attacking man, but some being hemophagous and some of their larvae invading human tissue.

Flies are subdivided into the suborder Orthorrhapha, with five families (Culicidae, Psychodidae, Ceratopogonidae, Simuliidae, and Tabanidae) of medical significance, and the suborder Cyclorrhapha with six families (Musicidae, Calliphoridae, Sarcophagidae, Oestridae, Hypodermatidae, and Gasterophilidae) of significance medically.

Family Culicidae (Mosquitoes): The subfamily Culicidae contains all the important species, the mouth parts being adapted for piercing and sucking blood. Adults have a globose head, long slender neck, narrowly elongate abdomen, long slender legs, and long, narrow wings. Males do not suck blood.

Mosquitoes have general medical significance because of their transmission of yellow fever, dengue, and malaria. They interest the dermatologist specifically because of the dermatitis produced by mosquito bites, their ability to transmit the microfilaria of Wuchereria bancrofti thus producing filariasis in some areas, and the production of cutaneous myiasis by the transmission of the Dermatobia hominis larva by several species of mosquitoes.

Genus Culex

Species C. pipiens (common house mosquito). It transmits filariasis in some areas.

Species C. fatigans. It replaces C. pipiens in tropical and subtropical areas.

Species C. tarsalis. It is widely distributed throughout western United States and is a fierce biter.

Genus Aedes

Species A. aegypti (yellow fever mosquito). It is also a transmitter of filariasis.

Species A. sollicitans (New Jersey or salt-marsh mosquito). The females are vicious biters.

Genus Psorophora

Species P. lutzii. It transmits the dermatobia hominis larva, producing cutaneous myiasis.

Family Psychodidae (Moth Flies, Owlet Midges, or Sand Flies): These are long-legged, small, moth-like, and densely clothed, with hairs and with oval or lanceolate-shaped wings. The subfamily Phlebotominae contains a single genus and is an important blood-sucker.

Genus Phlebotomus (sand flies). It is widely distributed throughout tropical and subtropical regions. There are only six species in North America, and it is not found north of a line from Washington, D. C., to San Francisco. The females are all blood-suckers. They cause sand fly bites.

Species P. papatasii. It transmits cutaneous leishmaniasis (Oriental sore), the agent being Leishmania tropica. It is also transmitted by P. sergenti and P. macedonicum.

Species (various) Phlebotomus. They transmit mucocutaneous leishmaniasis (American leishmaniasis), the agent being Leishmania brasiliensis.

Species P. verrucarum. It transmits Carrión's disease (verruga peruana, Oroya fever), the agent being Bartonella bacilliformis.

Family Ceratopogonidae: There are only four species sucking the blood of man.

Genus Culicoides (punkies, biting midges). These are minute blood-suckers, capable of passing through ordinary mosquito screens. This genus has a wide distribution in the tropics and temperate zone.

Species Culicoides dovei (salt-marsh punkie). It is a serious pest along the Atlantic seaboard and is representative of five species found widely distributed in North America. It causes punkie bites.

Family Simuliidae (Black Flies, Buffalo Gnats): These are minute flies, almost world-wide in distribution. Only the females are blood-suckers, being most active in daylight.

Genus Simulium. It causes black-fly bites. It transmits onchocerciasis, the agent being Onchocerca volvulus. Various species in tropical Africa and S. metallicum, S. ochraceum, and S. callidum in Guatemala and southern Mexico are transmitters of this disease.

Family Tabanidae (Horse Flies, Gad Flies): These are medium to very large thick-set bulky flies, with a wide head and brilliantly colored eyes. The females are blood-suckers in most species, while males take only plant juices. They are active on warm bright moist days. There are over 300 species in North America, mostly in the genus Tabanus, but the genus Chrysops is the only one of medical importance.

Genus Chrysops. It causes tabanid-fly bites, the painful wounds healing slowly. It transmits tularemia, the agent being Pasteurella tularensis (by the species C. discalis [deer fly]) and loaiasis (Calabar swelling), the agent being Loa loa (African eye worm) (by the species C. dimidiata [mangrove fly]).

Family Muscidae (Muscid Flies): Only a few genera are blood-suckers, and only one species which attacks man is cosmopolitan in distribution.

Species Stomoxys calcitrans (biting stable fly). It resembles the common house fly which does not bite man. It causes fly bites. Both male and female are vicious biters.

Family Calliphoridae (Blowflies): These are medium to large flies of a bright, uniform, metallic color. They lay eggs in decaying organic matter, but some species lay eggs in cutaneous sores, causing myiasis (infestation with larvae).

Genus Callitroga

Species C. americana (primary screw-worm fly). It is widely distributed from southern United States to Brazil and is an obligatory parasite. It causes cutaneous myiasis (wound myiasis). It is probably the chief cause of wound myiasis throughout its range.

Species C. macellaria (common American screw-worm fly). It is saprozoic rather than parasitic.

Genus Chrysomya

Species C. bezziana (also known as Cochliomyia bezziana). This is the common fly of Africa and Asia, related to our screw-worm fly. It causes cutaneous myiasis.

Genus Calliphora (blue-bottle flies). They cause wound infestation by maggots. Wound myiasis is semispecific, not obligatory.

Genus Cordylobia

Species C. anthropophaga (the tumbu fly). It is widely distributed in tropical Africa. It causes cutaneous myiasis (furuncular swelling).

Family Sarcophagidae (Flesh Flies): They are rather large thick-set grayish flies. There are few genera but numerous species, all larviparous.

Genus Wohlfahrtia

Species W. vigil (the nearctic flesh fly). It is widely distributed in eastern North America. The females are particularly attracted to young children for larviposition. It causes cutaneous myiasis. Healthy skin is attacked.

Family Oestridae (Warble Flies or Botflies): The larvae are parasitic in the nasal region and sinuses of sheep, goats, and other hoofed mammals. They are nonblood-sucking.

Species Oestrus ovis (sheep nasal botfly). It causes ophthalmomyiasis (the larvae cannot develop beyond the first stage in man) and myiasis of the nose and throat.

Family Hypodermatidae (Warble Flies or Botflies): These are large stout hairy flies which are usually tawny-colored and which resemble the bee.

Genus Hypoderma (cattle warble flies). They are usually parasites of cattle, the larvae invading the skin through the hair follicle.

Species H. bovis. They are found in the north temperate zone.

Species H. lineatum. They are found further south. They cause subcutaneous myiasis (not creeping eruption).

Family Gasterophilidae (Warble Flies or Botflies): They have a general likeness to honey bees, being large, brown, and hairy.

Genus Gasterophilus (horse warble flies).

Species G. intestinalis, species G. nasalis, and species G. haemorrhoidalis. They cause creeping eruption (Larva migrans). It is caused by all three species. It is a relatively uncommon infestation of humans.

Family Cuterebridae (Warble Flies or Botflies): The adults are rather large and appear like bees. Mouth parts are vestigial, as the adults never feed. These flies are abundant in Mexico, and in Central and South America.

Species Dermatobia hominis (human or tropical warble fly). The eggs are glued by the female to a mosquito or other blood-sucking arthropod. The larvae are liberated when a warm-blooded animal is attacked by the carrier and penetrate through the puncture wound, causing cutaneous myiasis.

STUDIES OF PLASMA CHANGES IN SKIN DISEASES BY PAPER CHROMATOGRAPHY

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WITHIN recent years increased attention has been paid to the changes in plasma proteins occurring in various disease processes. Such studies by means of electrophoresis [1] have yielded interesting and important results and have clearly shown the superiority of this method to the chemical determinations of protein fractions. However, the high cost of apparatus and the technical difficulties restrict the use of this method to relatively few research institutions, whereas a less costly and simpler method would permit investigations on a broader scale. It appears that such methods have been found in plasma chromatography on filter paper [2] and in microelectrophoresis.[3] This paper deals with the former method. The results of chromatographic investigations of the plasma of 250 patients suffering from various diseases and of 30 normal control persons are given, and the technique of plasma chromatography on filter paper is described.

By means of this new procedure it is possible to cause a spread of a small quantity of plasma proteins into a "pattern."[2] These patterns are characteristic for normal plasma and differ from those obtained with plasma of patients suffering from various disorders.

A small quantity of plasma is placed on filter paper and treated with an aqueous developing solvent. The proteins ascend the paper by capillary action [4] (Fig. 1*A* and *B*). The pattern is obtained by developing the chromatogram in the second dimension, using another aqueous solvent (Fig. 1*C*). Small quantities of surface-

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1. Tiselius, A.: A New Apparatus for Electrophoretic Analysis of Colloidal Mixtures, Tr. Faraday Soc. **33**:524, 1937.

2. Franklin, A. E., Quastel, J. H., and Van Straten, S. F.: Paper Chromatography of Protein Mixtures and Blood Plasmas, Proc. Soc. Exper. Biol. & Med. **77**:783, 1951.

3. Flynn, F. V., and de Mayo, P.: Micro-Electrophoresis of Protein on Filter-Paper, Lancet **2**:235, 1951.

4. Williams, R. J., and Kirby, H.: Paper Chromatography Using Capillary Ascent, Science **107**:481, 1948.

active agents such as polyoxyalkylene sorbitan monooleate ("Tween 81) or polyoxyalkylene sorbitan trioleate ("Tween 85) are added to the plasma in order to facilitate the formation of characteristic patterns. Hemin is added to the plasma before it is applied to the paper in order to label the protein. The chromatogram, after development in two dimensions, is treated with a benzidine-peroxide mixture which makes visible the position of the protein-hemin complex. The hemin may be omitted and the proteins located by use of a suitable dye, such as Solway purple,[5] azocarmine B, bromophenol blue, or naphthalene black 12B.[3] The patterns obtained by the two methods are almost identical. The hemin-benzidine method has been used in this investigation, and permanent records are made by photographing the chromatograms immediately after streaking.

PROCEDURE

Blood samples are withdrawn from fasting patients and mixed with heparin (0.1 ml. of a 1% solution of the heparin per 10 ml. of blood). The plasma is separated by centrifu-

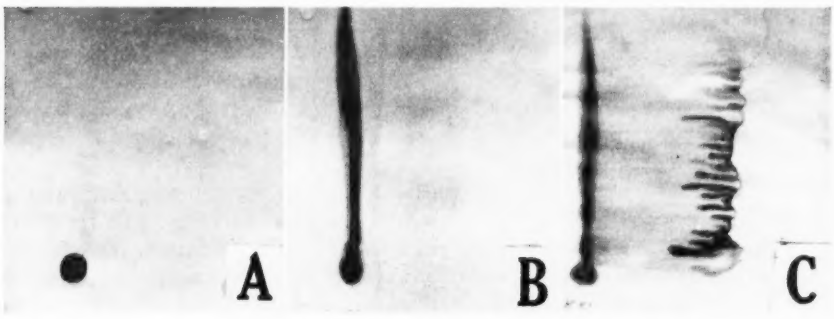

Fig. 1.—Two-dimensional filter-paper chromatography of plasma proteins. *A*, 0.02 ml. of plasma spotted and dried; *B*, developed in 0.1 M sucrose solution in the first dimension; *C*, developed in 0.1 M sodium potassium tartrate in the second dimension.

gation and 0.5 ml. portions pipetted into culture tubes containing 0.02 ml. of a 0.3% hemin solution (30 mg. of crystalline hemin in 10 ml. of a 3% sodium bicarbonate solution) and the required amount of polyoxyalkylene sorbitan monooleate (0.02 ml.) or polyoxyalkylene sorbitan trioleate (0.01 ml.). The contents of the tubes are well mixed, and 0.02 ml. aliquots are placed at the lower left-hand corner of the filter-paper squares. (Eight-inch [20.3 cm.] sheets of Whatman No. 1 filter paper are used throughout the work.) The papers are mounted on suitable racks or stapled into cylinders, after the spots are dried at room temperature, and then placed in a shallow dish containing 0.1 M sucrose solution, the developing agent used in the first dimension. After the papers are thoroughly wetted by capillary action (about one and one-half hours), they are dried at room temperature, turned at right angles, and placed into the second dimensional developing solvent (0.1 M sodium potassium tartrate solution) until the liquid has traveled approximately two-thirds up the paper. After drying, the papers are streaked with freshly prepared benzidine reagent (equal volumes of 3% hydrogen peroxide and a saturated alcoholic solution of benzidine acidified with glacial acetic acid) and photographed before the background color develops and obscures the pattern.

5. Jones, J. I. M., and Michael, S. E.: Chromatography of Proteins, Nature, London **165**:685, 1950.

INTERPRETATION OF CHROMATOGRAMS

Normal Patterns.—Plasma from normal persons gives rise to virtually identical patterns, characterized by many short distinct fractions extending, in the second dimension, from a position opposite the point of origin to a position opposite the top of the first dimensional streak (Fig. 2 *A* and *B*).

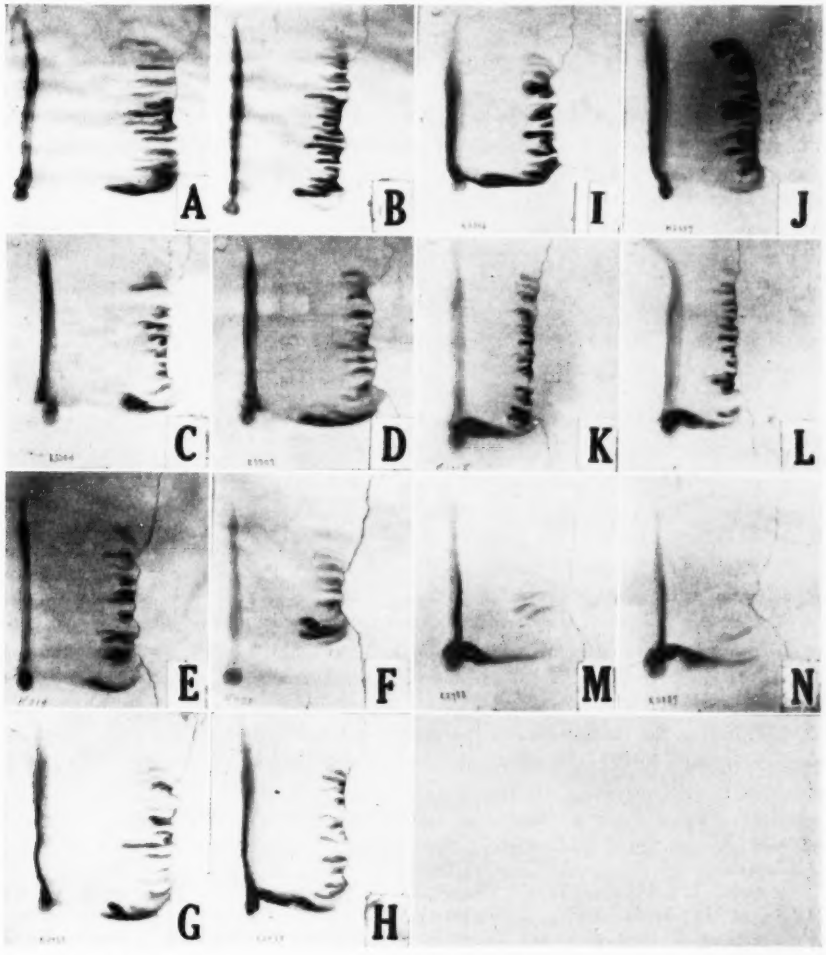

Fig. 2.—Normal and abnormal patterns and degrees of abnormality. *A, B,* normal plasma; *C, D, E, F,* first degree of abnormality (+); *G, H, I, J,* second degree of abnormality (++); *K, L, M, N,* third degree of abnormality (+++); *A, C, E, G, I, K, M,* (0.02 ml. of polyoxyalkylene sorbitan monooleate per 0.5 ml. plasma); *B, D, F, H, J, L, N,* (0.01 ml. of polyoxyalkylene sorbitan trioleate per 0.5 ml. plasma).

Abnormal Patterns and Degree of Abnormality.—Abnormal chromatogram patterns are found in plasmas with abnormal protein balances. The degree of abnormality is estimated by comparing these abnormal patterns with those found in normal controls.

The first degree of abnormality (+) represents patterns that vary only slightly from the normal. The lower fractions are heavier, but do not extend to the point of origin under either polyoxyalkylene sorbitan oleate condition (Fig. 2 *C* and *D*). Included in this group are also those cases in which patterns appear to be somewhat contracted (Fig. 2 *E* and *F*).

The second degree of abnormality (++) corresponds to those patterns in which the basal fractions trail from the point of origin under either one or other of the polyoxyalkylene sorbitan oleate conditions (Fig. 2 *G*, *H*, *I*, and *J*). This is sometimes accompanied by a reduction in the number and the heaviness of the upper fractions.

The third degree of abnormality (+++) is attributed to those patterns in which the basal fractions trail from the origin under both polyoxyalkylene sorbitan oleate conditions (Fig. 2 *K* and *L*). This increased heaviness of the lower fractions often occurs with a considerable decrease in number and heaviness of the upper fractions (Fig. 2 *M* and *N*).

Since it has been observed that deviations from the normal patterns occurred in those plasms in which a disturbance of the protein balance was present, it was thought advisable to study the chromatographic patterns of solutions of purified protein fractions in which the proportions of the various constituents could be changed at will.

CHROMATOGRAMS OF SYNTHETIC PLASMA MIXTURES

A solution may be prepared containing albumin, α, β, and γ globulins, and fibrinogen in the proportions that are found in the plasma of normal persons, using the appropriate quantities [6] of Cohn Fractions I, II, III-O, IV-4 and V [7] dissolved in 0.85% saline.

This solution, when chromatographed under the given conditions, gives rise to protein patterns closely resembling the patterns obtained with normal plasma (Fig. 3 *A* and *B*). That they are not identical is to be expected, since plasma contains constituents other than proteins, such as surface-active substances, which are known to alter the pattern [8] and which may be absent in the purified protein fractions.

By altering the proportions of the proteins in this mixture (Table 1) abnormal patterns result, resembling those obtained in the plasma of various pathological conditions. In mixtures 2, 3, and 4 (Table 1), γ, β, and α globulins respectively were increased and the amount of albumin proportionately decreased. The amount of fibrinogen remained unchanged in all solutions. In mixtures 5, 6, and 7 (Table 1),

6. Cohn, E. J.; Strong, L. E.; Hughes, W. L. Jr.; Mulford, D. J.; Ashworth, J. N.; Melvin, M., and Taylor, H. L.: Preparation and Properties of Serum and Plasma Proteins: A System for the Separation into Fractions of the Protein and Lipoprotein Components of Biological Tissues and Fluids, Am Chem. Soc. **68**:459, 1946.

7. Composition of Cohn Fraction I, 7% albumin, 8% α globulin, 15% β globulin, 9% γ globulin, 61% fibrinogen; composition of Cohn Fraction II, 3% β globulin, 97% γ globulin; composition of Cohn Fraction III-O, 6% albumin, 5% α globulin, 84% β globulin, 5% γ globulin; composition of Cohn Fraction IV-4, 16% albumin, 46% α globulin, 38% β globulin; composition of Cohn Fraction V, 95% albumin, 4% α globulin, 1% β globulin.

8. Swank, R. L.; Franklin, A. E., and Quastel, J. H.: Effect of Fat Meals and Heparin Administration in Blood Plasma Composition as Shown by Paper Chromatography, Proc. Soc. Exper. Biol. & Med. **75**:850, 1950.

the amount of the individual globulins was increased in each case, while the quantity of albumin remained the same as in the "normal" mixture. Chromatograms of the latter group (Fig. 3 *I*, *J*, *K*, *L*, *M*, and *N*) showed a greater deviation from the

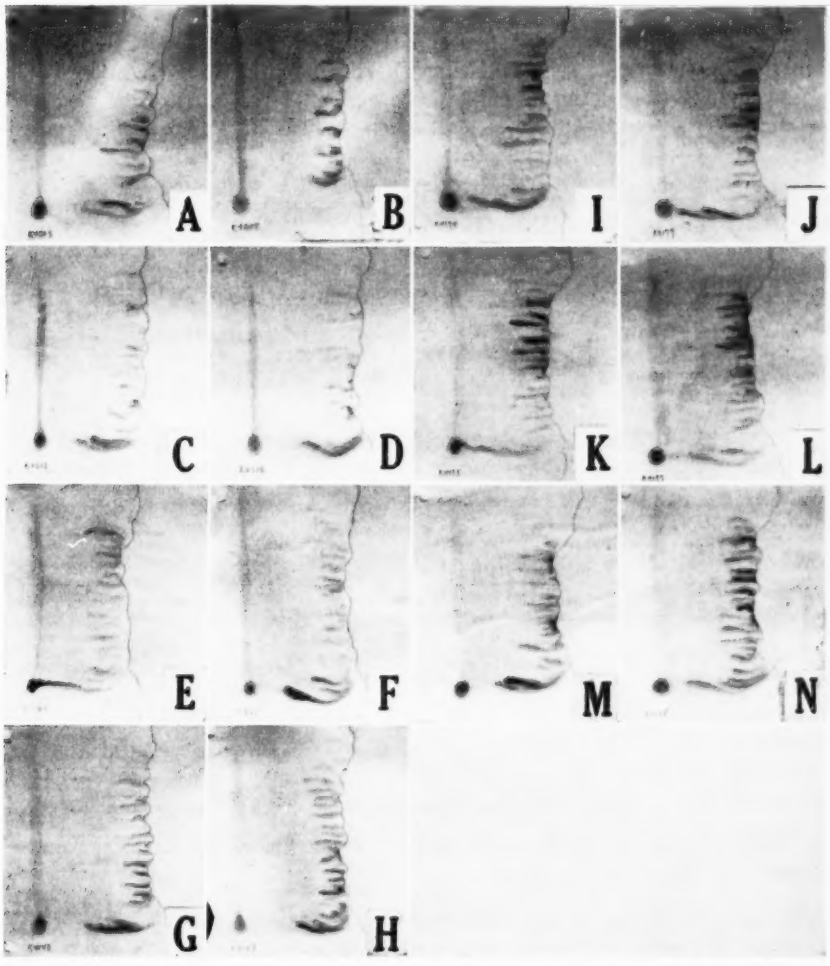

Fig. 3.—Synthetic plasma mixtures. *A*, *B*, mixture 1; *C*, *D*, mixture 2; *E*, *F*, mixture 3; *G*, *H*, mixture 4; *I*, *J*, mixture 5; *K*, *L*, mixture 6; *M*, *N*, mixture 7; *A*, *C*, *E*, *G*, *I*, *K*, *M*, (0.02 ml. of polyoxyalkylene sorbitan monooleate per 0.5 ml. of solution); *B*, *D*, *F*, *H*, *J*, *L*, *N* (0.01 ml. of polyoxyalkylene sorbitan trioleate per 0.5 ml. of solution).

"normal" patterns (Fig. 3 *A* and *B*) than those of the former group (Fig. 3 *C*, *D*, *E*, *F*, *G*, and *H*). An increase, however, in either α, β, or γ globulins gave rise to some abnormalities of the chromatograms in both groups. It would thus seem logical to associate the heavy basal fractions with an increase in one or more of the globulins. This does not mean that all the globulins appear in the lower tracks and

all the albumin in the upper fractions. In fact, we have been able to show a distribution of albumin and globulins throughout the patterns by means of microelectrophoresis on filter paper. However, there is a preponderance of globulin in the fractions of the lower part of the chromatogram, while albumin prevails in the upper fractions.[8a]

The mechanism of the formation of these patterns is not known as yet. The important feature is the fact that the changes in the chemical constitution of the plasma of patients suffering from various disorders are reflected in the abnormal protein patterns, and that these patterns are reproducible.

TABLE 1.—*Composition of Plasma Mixtures in Mg. per Ml.*

Mixture No.	1 Normal	2	3	4	5	6	7
Albumin	36.3	21.9	21.9	27.1	36.3	36.3	36.3
α Globulin	9.2	9.2	9.2	12.0	9.2	9.2	12.0
β Globulin	10.6	10.6	21.6	10.6	10.6	21.6	10.6
γ Globulin	7.2	21.6	7.2	7.2	21.6	7.2	7.2
Fibrinogen	2.7	2.7	2.7	2.7	2.7	2.7	2.7
Total protein	66.0	66.0	62.6	59.6	80.4	77.0	68.8
Grading of chromatogram	0	+	++	+	+++	++	+

TABLE 2.—*Paper Chromatogram in Skin Diseases*

Disease	Cases, No.	Chromatogram: Normal	Abnormal: +	++	+++
Normal controls	30	25	5	..	..
Lupus erythematosus					
Acute disseminated	5	..	2*	1	2
Subacute	2	..	..	..	2
Chronic discoid	13	7	1	4	1
Psoriasis					
Without arthritis	28	6	7	8	7
With arthritis	7	..	..	4	3
Dermatitis	22	8	7	4	3
Pemphigus vulgaris	7	..	2	2	3

* Two patients had received cortisone before test was performed.

The plasmas of 250 persons were studied by this technique and the accompanying Tables show some of our results.

CHROMATOGRAMS IN VARIOUS SKIN DISEASES AND IN NORMAL CONTROLS

The results shown in Table 2 demonstrate the uniformity of the pattern in healthy persons. Slight abnormalities were seen in five cases, which may constitute the range of normal variations, but which may also indicate the presence of some, as yet not manifest, metabolic disorder in these persons.

In none of the acute or subacute cases of lupus erythematosus was there a normal pattern; various degrees of abnormality were found in all. One of the patients (Case 14, Table 4) listed as (+) had already received cortisone therapy for four days,

8a. Quastel, J. H., and Van Straten, S. F.: Protein Separations and Interactions on Filter Paper, Proc. Soc. Exper. Biol. & Med. **81**:6, 1952.

which may have reduced the degree of abnormality. It is of interest to note that almost half the patients suffering from chronic lupus erythematosus showed abnormalities in varying degrees.

The same is true of the group of patients with psoriasis, and it may be particularly noted that the test showed marked abnormalities in all seven patients who suffered from a psoriasis associated with rheumatoid arthritis.

The dermatitis groups consisted of patients with atopic dermatitis and contact dermatitis but also included some in whom no exact etiological diagnosis was established. No significant differences in the incidence of abnormalities in these various groups were found. The impression was gained, however, that incidence and degree of chromatographic abnormalities were higher in the more extensive cases.

In all cases of pemphigus distinct abnormalities were shown, and the degree of abnormality was clearly related to the severity of the disease.

CHROMATOGRAPHY IN VARIOUS DISEASES

Examples of the diseases listed in Table 3 were investigated for the purpose of control, and the consistent pattern of abnormalities, correlated with the acuity and

TABLE 3.—*Paper Chromatogram in Various Diseases*

Disease	Cases, No.	Chromatogram			
			Abnormal		
		Normal	+	++	+++
Rheumatoid arthritis	14	1	3	4	6
Rheumatic fever	3	..	..	..	3
Diseases of the liver	15	..	4	6	5
Malignant conditions	17	4	..	7	6

severity of the disorders, may suggest the usefulness of this method for the investigation of many disorders.

The additional 90 cases, not shown in Table 3, comprised a variety of disorders. The chromatographic patterns obtained were largely consistent with the diagnosis. Two cases of scleroderma were investigated, in both of which abnormal patterns were shown. Advanced heart disease and general infections gave abnormal patterns, while peptic ulcers, diabetes, and other endocrine disorders showed no abnormalities.

CORRELATION OF CHROMATOGRAMS WITH OTHER TESTS IN LUPUS ERYTHEMATOSUS

Table 4 lists the group of patients with lupus erythematosus showing abnormal chromatographic findings. An abnormal pattern was obtained in all patients with an abnormal albumin-globulin ratio, determined by the Howe method.[9] However, several abnormal chromatograms were found in patients in whom the chemical tests were normal. Complete hemograms and search for L. E. cells and phenomenon were carried out in all the acute and subacute cases. No correlation was found between the chromatograms and either the leucocyte count, the sedimentation rate, or the L. E. phenomenon.

9. Howe, P. E.: The Use of Sodium Sulfate as the Globulin Precipitant in the Determination of Proteins in Blood, J. Biol. Chem. **49**:93, 1921.

CHROMATOGRAMS BEFORE AND AFTER THERAPY IN LUPUS ERYTHEMATOSUS AND IN PEMPHIGUS

Table 5 demonstrates, unequivocally, a return to normal of the chromatograms in all cases after treatment (see also Fig. 4). Corticotropin (ACTH) or cortisone was used in nine cases and calcium pantothenate in two. Therapy was attended with clinical improvement in all cases.

TABLE 4.—*Correlation of Chromatograms with Other Tests in Lupus Erythematosus*

		Paper Chromatogram					Chemical Determination (Howe) Gm. Per 100 Cc.		
Case	Form of L. E.	Norm.	+	++	+++	L. E. Phenomenon	Total Protein	Albumin	Globulin
1	Acute disseminated	..	..	..	X	Marked	7.20	3.45	3.75
2	Acute disseminated	..	..	..	X	Absent	7.42	2.99	4.43
14	Acute disseminated	..	X	..	..	Moderate	5.98	2.99	2.99
20	Acute disseminated	..	..	X	..	Absent	7.56	2.45	5.11
24	Acute disseminated	..	X	..	..	Present	7.56	2.22	5.34
3	Subacute	..	..	..	X	Absent	6.92	5.06	1.86
6	Subacute	..	..	..	X	Absent	8.00	4.62	3.38
15	Chronic discoid	..	..	X	..	Absent	....	....	....
11	Chronic discoid	..	..	..	X	.....	7.96	5.65	2.31
4	Chronic discoid	..	X	..	..	.....	7.80	5.06	2.74
18	Chronic discoid	..	..	X	..	.....	7.66	4.31	3.35
19	Chronic discoid	..	X	..	..	.....	6.96	4.61	2.35

TABLE 5.—*Effect of Treatment on Chromatogram*

	Before Treatment				After Treatment			
Diagnosis	Norm.	+	++	+++	Norm.	+	++	+++
L. E. acute disseminated	..	..	..	X	..	X	..	..
L. E. acute disseminated	..	..	..	X	..	X	..	..
L. E. subacute	..	..	..	X	..	X	..	..
L. E. chronic discoid	..	..	X	..	X	..	..	..
L. E. chronic discoid	..	..	..	X	..	X	..	..
Pemphigus vulgaris	..	..	..	X	..	X	..	..
Pemphigus vulgaris	..	X	..	..	X	..	..	..
Pemphigus vulgaris	..	..	X	..	X	..	..	..
Pemphigus vulgaris	..	..	..	X	X	..	..	..
Pemphigus vulgaris	..	..	..	X	X	..	..	..
Pemphigus vulgaris	..	..	..	X	X	..	..	..

COMMENT

Comparison with Other Methods of Protein Investigation.—All plasmas with an abnormal albumin-globulin ratio (Howe method) have produced abnormal chromatograms. Abnormal chromatographic patterns, however, have been found in several cases with normal albumin-globulin ratios. Petermann, Young, and Hogness [10] have noted similar discrepancies when comparing results obtained by electrophoretic methods (Tiselius) with those obtained by the Howe method. They pointed out that with the Howe method α globulins are not precipitated but remain in solution

10. Petermann, M. L.; Young, N. F., and Hogness, K. R.: Comparison of the Howe and Electrophoretic Methods for the Determination of Plasma Albumin, J. Biol. Chem. **169**:379, 1947.

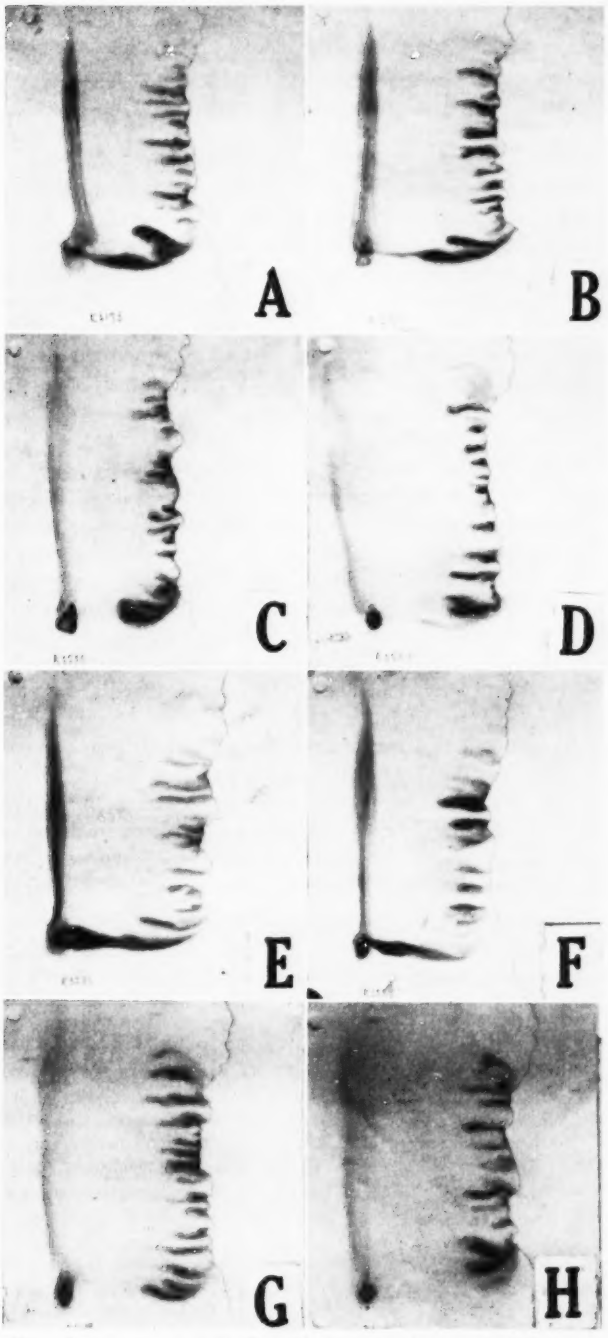

Fig. 4.—Effect of treatment. *A*, *B*, Case 18, lupus erythematosus before treatment; *C*, *B*, Case 18, after treatment; *E*, *F*, Case 60, pemphigus vulgaris, before treatment; *G*, *H*, Case 60, after treatment; *A*, *C*, *E*, *G*, (0.02 ml. of polyoxyalkylene sorbitan monooleate per 0.5 ml. of plasma); *B*, *D*, *F*, *H*, (0.01 ml. of polyoxyalkyline sorbitan trioleate per 0.5 ml. of plasma).

with the albumin and are included in the albumin estimation. We have performed chemical tests on various mixtures of purified plasma proteins, containing known quantities of the various fractions, and our results have confirmed Petermann's findings.

Several studies on plasma proteins in skin diseases by means of electrophoresis (Tiselius apparatus) have been published lately.[11] Walker and Benditt,[11b] as well as Leven,[11d] found a decrease in albumin and an increase in γ globulin as the characteristic features of lupus erythematosus. These changes were more marked in the acute disseminated forms than in the chronic discoid form, and Lever [11d] found several cases of the latter group in which there was a normal electrophoretic pattern. A similar incidence of abnormalities has been obtained with our method. In all the cases of acute or subacute lupus erythematosus an abnormal chromatographic pattern was shown. The extent of the abnormality was largely consistent with the severity of the disease process. Of our 13 cases of chronic discoid forms, in 7 there was a normal pattern, while abnormalities were noted in 6.

Lever [11d] stated that the increase in γ globulin occurs early in the disease. We could confirm Lever's statement with our method in three of our patients, in whom marked chromatographic abnormalities were noted immediately after the first signs of clinical activity.

The reports on plasma protein disturbances in psoriasis are conflicting. Some authors, using the Howe method, found normal values,[12] while others, using the same method, reported low globulin and high albumin values.[13a,b] Charpy [13c] found an increase in globulins prior to and during eruptions. Thirty-five patients were studied by the chromatographic method, 29 of whom showed abnormalities suggestive of an increase in some globulin. The abnormalities were particularly marked in those patients in whom an associated rheumatoid arthritis was present. Lever [11d] studied six cases by the Tiselius method, and an increase in α globulin was noted in five instances. In view of the above-mentioned shortcomings of the Howe method, we suggest that the apparent increase in albumin reported by some authors is in fact an increase in α globulin. The high percentage of abnormal findings in our series was an unexpected finding which may deserve further investigations.

Clinical Applications of the Chromatographic Method.—It may as yet be too early to attempt definite conclusions regarding the practical usefulness of this method. It is generally recognized that no method of investigation of plasma proteins has a specific diagnostic value, since heterogeneous diseases may give rise

11. (*a*) Robert, P.: Serumuntersuchungen, insbesondere mit der Elektrophorese, bei verschiedenen Hautkrankheiten, Dermatologica **97 (supp)** :89, 1948. (*b*) Walker, S. A., and Benditt, E. P.: The Serum Proteins in Diseases of Connective Tissue, J. Invest. Dermat. **14**:113, 1950. (*c*) Lever, W. F.: The Proteins in Pemphigus Vulgaris, ibid. **14**:205, 1950. (*d*) Lever, W. F.; Schultz, E. L., and Hurley, N. A.: Plasma Proteins in Various Diseases of the Skin, A. M. A. Arch. Dermat. & Syph. **63**:702, 1951. (*e*) Leinbrock, A.: Veränderungen der elektrophoretischen Proteinspektren im Serum und in der Blasenflüssigkeit und Verhalten der Serum labilitätsteste bei verschiedenen Phemphigusformen, Arch. Dermat. u. Syph. **192**:535, 1951.

12. Mulvehill, W.: Serum Protein in Dermatoses, Arch. Dermat. & Syph. **49**:327, 1944.

13. (*a*) Pulay, M. E.: Le Psoriasis vulgaris et son traitement, Bull. Soc. Franç. dermat. et syph. **43**:1,508, 1936. (*b*) Desaux, A.; Goiffon, R., and Pretet, H.: Contribution a l'étude des protides du serum dans le psoriasis, ibid. **47**:50, 1940. (*c*) Charpy, J.: Le problème du psoriasis, Presse méd. **58**:283, 1950.

to identical protein changes. At the same time, in many instances, an objective measuring of plasma protein disturbances may provide additional aid in the assessment of obscure and ill-defined signs and symptoms. We feel justified, however, in suggesting the usefulness of protein chromatography in the evaluation of the activity of a disease process in which protein changes are prone to occur. We believe that this may be so, because abnormalities in the chromatographic patterns in lupus erythematosus appear immediately after the onset of clinical signs of activity, because the degree of abnormality is clearly related to the clinical activity, and, finally, because the chromatographic pattern reverts to normal after therapy. Further work may indicate the usefulness of periodic chromatographic examinations of clinically inactive patients with lupus erythematosus and other disorders.

This inexpensive method can also be used as a screening test for large numbers of samples of various diseases, some of which may then be submitted to quantitative protein separations by the Tiselius method.

SUMMARY

The technique of protein chromatography on filter paper is described.

Almost identical patterns are obtained with the plasmas of normal persons.

Different and reproducible patterns are found with the plasmas of patients with various disease processes. These abnormalities are described, and the degree of abnormality is defined.

Chromatograms of solutions of purified protein fractions in proportions corresponding to normal plasma give rise to patterns closely resembling the normal plasma patterns.

Increase of α, β, or γ globulin results in patterns closely resembling those found in the plasma of certain disease processes.

Two hundred fifty human plasmas have been investigated by this method. Consistently abnormal patterns have been found in all cases of acute and subacute lupus erythematosus and in pemphigus. Chronic discoid lupus erythematosus, psoriasis, rheumatoid arthritis, diseases of the liver, and cancers give a high proportion of abnormal patterns.

The incidence and the degree of abnormalities are clearly related to the activity of the disease process.

Therapy results in prompt reversal to normal of the chromatographic pattern in lupus erythematosus and in pemphigus.

The chromatographic method has no specific diagnostic value, but permits an assessment of the activity of a disease process in which protein changes are prone to occur.

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AUTOSENSITIZATION DERMATITIS

Discussion and Protocol of an Experiment

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THE CONCEPT of autosensitization, whereby a person becomes sensitized in one or more of his organs to a substance elaborated from his own tissue proteins, has been a stimulating subject for investigation in the past decade.

Whitfield [1] was probably the first to apply this concept to the field of dermatology. In 1921, he reported the cases of two patients in whom generalized toxic eruptions appeared approximately 10 days after the occurrence of traumatic hematomas. A generalized papular, urticarial eruption developed in a third patient 11 days after the acute exacerbation of a dermatitis of the legs. In another patient, a red-streaked urticarial wheal developed whenever serum from a vesiculobullous eczema of the legs came in contact with normal areas of the skin. For these peculiar phenomena, Whitfield coined the term "autosensitization."

In 1929, Dennie, McBride, and Davis [2] noted the occurrence of a generalized exfoliative dermatitis complicating a localized eruption treated with trinitrophenol. They expressed the opinion that the generalized dermal reaction was due to a sensitization to "protein picrinate" elaborated at the site of the burn and carried by the blood stream.

Hopkins and Burky,[3] in 1944, reviewed the various "ids" and pointed out that they are autosensitization phenomena; they believed that many eczemas of the hands are due to a sensitization to a combination of the patient's own keratin and Staphylococcus toxin. They reported good therapeutic results following desensitization with Staphylococcus toxin.

Smith,[4] in 1945, reported a case of "eczema autolytica" occurring in a patient with chronic eczema of the legs, who experienced exacerbation of the local process, followed in a week or two by the development of a generalized papulovesicular eruption. He thought that a dermolysin was formed at the site of the primary eruption and considered it to be a foreign bacterial protein, a substance derived from tissue breakdown, or a combination of the two.

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2. Dennie, C. C.: McBride, W. L., and Davis, P. E.: Toxic Reactions Produced by the Application of Trinitrophenol (Picric Acid), Arch. Dermat. & Syph. **20**:698 (Nov.) 1929.

3. Hopkins, H. H., and Burky, E. L.: Cutaneous Autosensitization: Role of Staphylococci in Chronic Eczema of the Hands, Arch. Dermat. & Syph. **49**:124 (Feb.) 1944.

4. Smith, S. W.: Eczema Autolytica, Brit. M. J. **1**:628 (May 5) 1945.

From 1944 to 1948, Simon [5] published several articles on the study of patients with atopic eczema. He found that positive patch and scratch tests could frequently be elicited with the use of normal and homologous scalp and body dander; antigenicity was further supported by antibody-neutralizaton tests. An interesting observation was the occurrence of positive reactions to homologous body and scalp dander in a newborn infant, suggesting that the reactions were not caused by bacterial contamination.

Additional evidence that circulating antibodies might develop during sensitization to homologous dander was presented by Hecht, Sulzberger, and Weil.[6] These investigators, working with rabbits, found that precipitins to homologous skin antigen could be produced by repeated intramuscular injection of Staphylococcus toxin and the skin antigen, but not to the latter substance alone.

In 1948, Templeton, Lunsford, and Allington,[7] working with human beings, were able to demonstrate the formation of precipitins after three or four injections of homologous whole-skin extract in five subjects.

Sabin,[8] over 20 years ago, demonstrated the transportation of a dye-protein antigen by leucocytes to the site of antibody formation in the reticuloendothelial system. Godlowski,[9] in 1948, reported that antigen is transported only by eosinophilic leucocytes.

Further attempts at elucidation of the mechanism of autosensitization were undertaken recently by Cormia and Esplin.[10] Their studies consisted of the intradermal testing of patients with autosensitization to the following materials:

1. Solution of ether-extracted skin scrapings, taken from a site adjacent to the "primary" eruption.

2. A suspension of the patient's leucocytes (two series, one group with eosinophilia and one without).

3. The patient's plasma.

4. Fluid from an induced cantharides blister.

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5. Simon, F. A.: Skin Reaction to Patch Test with Human Dander, Ann. Allergy **2**:109 (March-April) 1944; On the Allergen in Human Dander, J. Allergy **15**:338 (Sept.) 1944; Human Dander: An Important Cause of Infantile Eczema, J. A. M. A. **125**:350 (June 3) 1944; Cutaneous Reactions of Persons with Atopic Eczema to Human Dander: Results of Patch Tests on Scarified Skin, Arch. Dermat. & Syph. **51**:402 (June) 1945; A Study of Atopic Eczema: I. Further Observations on Allergy to Human Dander; II. Cutaneous Reactions to Eczema Scales, Ann. Allergy **6**:584 (Sept.-Oct.) 1948.

6. Hecht, R.; Sulzberger, M. B., and Weil, H.: Studies in Sensitization to Skin: I. The Production of Antibodies to Skin by Means of the Synergistic Action of Homologous Skin Antigen and Staphylococus Toxin, J. Exper. Med. **78**:59 (July) 1943.

7. Templeton, H. J.; Lunsford, C. J., and Allington, H. V.: Autosensitization Dermatitis: Report of 5 Cases and Protocol of an Experiment, Arch. Dermat. & Syph. **59**:68 (Jan.) 1949.

8. Sabin, F. R.: Cellular Reactions to a Dye-Protein with a Concept of the Mechanism of Antibody Formation, J. Exper. Med. **70**:67 (July) 1939.

9. Godlowski, Z. Z.: Transportation of the Anaphylactogenic Property by Eosinophils, Brit. J. Exper. Path. **29**:511 (Dec.) 1948.

10. Cormia, F. E., and Esplin, B. M.: Auto-Eczematization: Preliminary Report, Arch. Dermat. & Syph. **61**:931 (June) 1950; Further Studies in Autoeczematization, A. M. A. Arch. Dermat. & Syph. **64**:31 (July) 1951.

Results showed that some type of reaction, positive or delayed, occurred approximately as follows:

1. Skin scrapings, 79%.
2. Leucocyte suspension: unselected, 30%; with eosinophilia, 50%.
3. Plasma, 10%.
4. Cantharides-blister fluid, 100%; however, identical results were obtained with controls.

Five patients with eosinophilia were given injections of 1 cc. of a 1:1,000 epinephrine solution. Within three hours, three of the patients experienced a definite exacerbation of their cutaneous disease.

In summarizing the results of their studies, the authors made the following statements:

1. "Autoeczematization" is considered to be a true allergic reaction.
2. The antigen responsible for the distal eczematous response is apparently a water-soluble fraction of epidermal cells.

TABLE 1.—*Distribution of Primary Dermatoses in Patients Studied*

Dermatosis	Total
1. Stasis dermatitis	7
2. Atopic dermatitis	2
3. Nummular eczema of hands	2
4. Seborrheic dermatitis	3
5. First-degree sunburn of exposed surfaces	1
6. Pellagra (exposed surfaces)	2
7. Dyshidrosis (palms and soles)	2
8. Contact dermatitis	10
(*a*) Hair dye (scalp)	1
(*b*) Elastic (trunk)	1
(*c*) Poison Oak (arms and legs)	2
(*d*) Merbromin (Mercurochrome) (arm)	1
(*e*) Adhesive tape (chest)	1
(*f*) Paint thinner (thighs)	1
(*g*) Soap and detergents (hands)	2

3. The development of immediate and delayed responses to intradermal injection of the antigen suggests that both fixed and circulating antibodies are present.
4. There is suggestive, although inconclusive, evidence that the antigen is transported from the primary site by eosinophilic leucocytes.

In evaluation of skin-test responses to cutaneous scrapings, it is apparent that the latter do not consist of epidermal cells only, as Cormia and Esplin have implied. Other components to be considered are contaminating surface bacteria, migratory leucocytes, and keratin. Scrapings from an inflamed area of skin would naturally be expected to contain a proportionately greater amount of bacteria and leucocytes than a normal site. In the study of cutaneous autosensitization, where one is frequently dealing with an acute, exudative, inflammatory "primary" focus, these two factors assume great importance as antigenic possibilities. It seemed worth-while, therefore, to modify and add to Cormia and Esplin's work.

MATERIALS AND METHODS

In this study, 28 patients were utilized, all with definite clinical evidence of widespread cutaneous autosensitization. The primary dermatoses were varied (Table 1); usually more than one secondary factor seemed to be operating in the induction of

autosensitization, i. e., local "overtreatment," secondary infection, trauma from scratching, and stasis.

Of the 28 patients, 16 were utilized for Part A and Part B of the study; 12 were used for Part C.

Part A consisted of the following procedures:

1. Intradermal testing of each patient to an aqueous suspension of skin scrapings taken from the primary focus, from an area adjacent to it, and from distant, grossly normal skin.
2. The bacterial culture of skin scrapings from the primary site and intradermal skin testing of these organisms.
3. Intradermal skin testing of each patient to a suspension of homologous blood leucocytes.
4. Precipitin tests utilizing these prepared suspensions as antigens and the patient's serum as a source of antibodies.

It is to be noted here that the "primary focus," though always acutely inflammatory, was infrequently exudative or grossly infected.

Part B consisted of the intradermal testing of each patient with incubated mixtures of skin scrapings from the primary site and the bacterial suspension, the bacterial and leucocyte suspensions, and the leucocyte suspension and skin scrapings from the primary site.

Part C consisted of the intradermal testing of 12 patients to the following incubated materials derived from a control:

1. A suspension of heat-killed bacteria cultured from the skin.
2. A leucocyte suspension.
3. A suspension of skin scrapings.
4. A mixture of bacterial and leucocyte suspensions.
5. A mixture of suspensions of leucocytes and skin scrapings.
6. A mixture of suspensions of bacteria and skin scrapings.

Preparation of Skin Scrapings.—All cutaneous scrapings were prepared by the method of Cormia and Esplin, as follows: Material was collected from uncleaned skin with a scalpel, washed with ether four times, suspended in isotonic sodium chloride solution, and refrigerated for 48 hours before use. The concentration of such suspensions was made as constant as possible by the addition of a known amount of isotonic sodium chloride solution into a fixed volume of vial and adding enough scrapings to fill "up to the mark." All suspensions composed partly or entirely of skin scrapings were rendered sterile before use by the addition of 0.5% phénol.

Preparation of Leucocyte Suspensions.—Venous blood, 15 cc., was placed in an oxalated tube and centrifuged for 20 minutes. The buffy coat was then extracted, further purified by centrifugation in a Wintrobe hematocrit tube, and placed in a vial containing 0.5 cc. of sterile isotonic sodium chloride solution.

Preparation of Bacterial Suspensions.—Cutaneous scrapings collected from the primary site of dermatitis were added to thioglycollate beef broth for growth. Colonies were isolated on blood agar and then transferred to tryptose agar. From this medium, bacteria were extracted by washings with saline solution. Suspensions thus made were kept at roughly equivalent concentrations by approximating their density to that of a standard typhoid-paratyphoid vaccine containing 1,000,000,000 organisms per cubic centimeter. After the necessary dilution with saline solution, the suspension was rendered sterile by heating in a water bath at 65 C. for one hour. It should be noted here that all cultures were grown aerobically.

Performance of Precipitin Tests.—Each suspension tested, in the amount of 0.5 cc., was layered onto an equal volume of the patient's blood serum, in various dilutions. A definite turbidity or formation of a precipitate at the interphase within 60 minutes was interrupted as a positive reaction.

TABLE 2.—*Part A: Individual Homologous Suspensions*

Patient No.	Primary Site: I. D. Testing Immed.	Primary Site: I. D. Testing Delayed	Primary Site: Precipitin Test	Site Adjacent to Primary: I. D. Testing Immed.	Site Adjacent to Primary: I. D. Testing Delayed	Site Adjacent to Primary: Precipitin Test	Normal Skin: I. D. Testing Immed.	Normal Skin: I. D. Testing Delayed	Normal Skin: Precipitin Test
1	1+	1+	1+ (1:10)	2+	1+	1+ (1:10)	1+	0	0
2	0	1+	0	1+	0	0	0	0	0
3	2+	1+	0	1+	0	0	0	0	0
4	3+	1+	1+ (1:10)	2+	0	1+ (1:10)	0	0	0
5	1+	0	0	0	0	0	0	0	0
6	2+	2+	1+ (1:10)	0	1+	0	0	0	0
7	1+	0	2+ (1:20)	0	0	0	0	0	0
8	4+	1+	3+ (1:40)	2+	1+	2+ (1:20)	0	0	0
9	1+	1+	0	0	0	0	0	0	0
10	1+	1+	0	1+	1+	0	0	0	0
11	0	0	0	0	0	0	0	0	0
12	0	0	0	2+	1+	0	0	0	0
13	2+	1+	1+ (1:10)	1+	1+	1+ (1:10)	1+	0	0
14	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0
16	1+	0	0	1+	1+	0	1+	0	0
Total +	11	9	6	9	7	4	3	0	0
Controls	2	0	0	1	0	0	0	0	0
Reactions	75%			62%			19%		

Patient No.	Bacterial Suspension Culture	I. D. Testing Immed.	I. D. Testing Delayed	Precipitin Test	W. B. C. Suspension: I. D. Testing Immed.	W. B. C. Suspension: I. D. Testing Delayed	W. B. C. Suspension: Precipitin Test
1	Streptococcus viridans	3+	1+	2+ (1:20)	0	0	0
2	N. C.* Staphylococcus albus	2+	1+	1+ (1:10)	1+	0	0
3	N. C. Staphylococcus albus	4+	3+	2+ (1:20)	2+	1+	0
4	N. C. Staphylococcus albus	1+	1+	4+ (1:80)	0	0	0
5	Staphylococcus aureus, coag. pos.	2+	1+	4+ (1:80)	0	0	0
6	N. C. Staphylococcus albus + Esch. coli	2+	1+	2+ (1:20)	0	0	0
7	N. C. Staphylococcus albus	3+	2+	2+ (1:20)	0	0	0
8	Proteus	0	0	1+ (1:10)	0	0	0
9	N. C. Staphylococcus albus	2+	1+	1+ (1:10)	0	1+	0
10	N. C. Staphylococcus albus	2+	1+	0	0	0	0
11	Staphylococcus citreus	1+	1+	0	0	0	0
12	N. C. Staphylococcus albus	1+	0	0	0	0	0
13	N. C. Staphylococcus albus	4+	2+	3+ (1:40)	1+	1+	0
14	N. C. Staphylococcus albus + aerobacter	0	0	0	1+	0	0
15	N. C. Staphylococcus albus + Esch. coli	2+	1+	2+ (1:20)	2+	1+	0
16	N. C. Staphylococcus albus	1+	1+	3+ (1:40)	0	0	0
Total +		14	13	12	5	4	0
Controls		1	2	0	0	0	0
Reactions		93%			38%		

* Noncoagulase.

Incubated Suspensions.—Equal volumes of individual suspensions were mixed together and incubated for 24 hours at 37 C. before testing.

Sites for Skin Testing.—The commonest locations chosen were the upper flanks and back, since these areas were most consistently free from the autosensitization eruption. In all instances, 0.1 cc. of suspension was injected as the test dose.

Interpretation of Cutaneous Reactions.—The following criteria were used for denoting positive reactions: (*a*) anything larger than a 0.5-cm. wheal with or without erythema present 30 minutes after the injection (immediate reaction); (*b*) anything larger than a 0.5-cm. zone of papulation or induration present 36 to 48 hours after the injection (delayed reaction).

The degree of reaction was interpreted as 1 to 4 +.

TABLE 3.—*Part B: Incubated Homologous Suspensions*

Patient No.	Bacteria and Leucocytes		Leucocytes and Skin Scrapings		Bacteria and Skin Scrapings	
	Immed.	Delayed	Immed.	Delayed	Immed.	Delayed
1	2+	1+	0	0	2+	1+
2	1+	0	1+	1+	3+	3+
3	2+	2+	0	0	2+	2+
4	1+	1+	0	0	2+	1+
5	2+	1+	1+	1+	2+	1+
6	0	0	0	0	3+	2+
7	0	0	0	0	2+	1+
8	2+	0	2+	1+	1+	0
9	1+	1+	0	0	3+	2+
10	1+	1+	0	0	1+	1+
11	2+	0	0	0	2+	1+
12	2+	1+	2+	1+	1+	1+
13	1+	1+	1+	1+	1+	0
14	0	0	0	1+	0	0
15	0	0	1+	1+	0	0
16	0	0	0	0	1+	1+
Total +	11	8	6	7	14	12
Controls	1	1	1	2	2	1
Reactions	69%		44%		87%	

TABLE 4.—*Reactions to Test Substances*

	No. Tested	Bact. Suspension *		Bact. & W. B. C. Suspensions		Suspension of Bact. & Skin Scrapings	
		Immed.	Delayed	Immed.	Delayed	Immed.	Delayed
Patients	12	2	1	3	1	6	6
Controls	20	1	0	0	0	1	1
Reactions (Immed. or delayed)		16%		25%		50%	

* Coagulase-negative Staph. albus.

Controls.—In Parts A and B of the study, one control was tested for each substance utilized. The sizable number of suspensions (total of 128) precluded a large control series.

In Part C, 20 controls were tested for each substance utilized (total of 5).

Part C, which deals with substances derived from a control, is not completely tabulated because the results can be summarized more simply.

There were no positive intradermal test reactions (immediate or delayed) to a suspension of leucocytes, a suspension of skin scrapings, or an incubated mixture of the two.

A summary of the reactions to the other test substances is shown in Table 4.

ELUCIDATION OF RESULTS

In order to simplify expression of the results, a positive immediate and/or delayed skin-test reading was arbitrarily considered as a positive reaction. Further translation of these results into percentages allows values to be more easily compared, as follows:

Part A, Individual Homologous Suspensions:
- Skin scrapings from primary site, 75%.
- Skin scrapings from area adjacent to primary site, 62%.
- Skin scrapings from distant normal site, 19%.
- Bacteria, 93%.
- Leucocytes, 38%.

Part B, Incubated Homologous Suspensions:
- Bacteria and leucocytes, 69%.
- Skin scrapings and leucocytes, 44%.
- Skin scrapings and bacteria, 93%.

Part C, Individual and Incubated Suspensions Derived From Control:
- Leucocytes, 0%.
- Skin scrapings, 0%.
- Bacteria, 16%.
- Bacteria and leucocytes, 25%.
- Bacteria and skin scrapings, 50%.
- Leucocytes and skin scrapings, 0%.

COMMENT ON RESULTS

From an analysis of the percentage values of Part A, it is apparent that positive intradermal reactions to homologous skin scrapings are statistically more frequent if the scrapings are taken from the primary, inflammatory site than if they are from a normal area. This fact might conceivably be caused by sensitization to one or more of the following factors: (*a*) normally nonpathogenic surface bacteria and contaminants, which are present in greater numbers at an inflamed, weeping, crusted site; (*b*) leucocytes, which are present in great numbers and are being proteolyzed to form new compounds, which serve as antigens; (*c*) substances derived from altered plasma protein, keratin, and damaged epithelial cells as a results of the inflammatory process; (*d*) formation of conjugated compounds through interaction of these factors.

The 38% incidence of positive intradermal reactions to homologous leucocyte suspensions conforms roughly to that obtained by Cormia and Esplin. These authors postulated that leucocytes are transporters of the autosensitizing antigen from its site of formation, through the blood, to the reticuloendothelial system.

Such a hypothesis ignores the possibility of leucocytes per se as being antigenic, rather than transporters, through proteolysis and conjugation with other substances at the primary site. In Parts B and C, attempts are made to elucidate this problem further.

The results of intradermal reactions to bacteria grown from the primary site are most impressive. The significance is even greater when one considers that, with few exceptions, Staphylococcus albus, coagulase-negative, was isolated. This organism is considered one of the common constituents of normal skin flora. The skin testing of 12 patients to a suspension of coagulase-negative Staph. albus obtained from the skin of a normal person elicited 25% positive reactions. The discrepancy

between this value and that obtained with homologous suspensions cannot be explained by chance alone. It seems likely that substances present at the site of an acute dermatitis, whether they be altered enzymes, leucocytes, plasma proteins, epidermal cells, or keratin, modify the reactivity and possibly the virulence of bacteria which are present. The converse, of course, should also be considered, i. e., that bacteria may alter the reactivity and antigenicity of other components present in an area of acute inflammation.

Precipitin testing was utilized in Part A of the experiment partially as a control method but primarily to substantiate the results of intradermal testing. Although not as sensitive as the latter, it was more specific. In general, positive precipitin reactions occurred when the corresponding antigen produced a strongly positive "immediate" type of intradermal response. This fact offers further evidence that there is a detectible circulating antigen responsible for autosensitization.

Part B of this study represents an attempt to determine whether various combinations of homologous epidermal cells and keratin, coagulase-negative Staph. albus, and leucocytes will add to the antigenicity of any single component. At best, the method is admittedly crude and represents in vitro testing. Its rationale is an effort to imitate in vivo conditions.

When evaluating the results one has to take into consideration (1) the factor of dilution of each substance in the mixture and (2) the simple additive antigenicity of each combination.

Once these items have been considered, it is apparent that the only antigenic "synergism" is produced by an incubated mixture of bacteria and skin scrapings taken from normal-looking skin. This observation suggests that, in vivo, the long-continued association of nonpathogenic bacteria and degenerating and inflamed epidermal cells or keratin, incubated together at body temperature in serum and tissue fluid, may be the source of the antigen responsible for autosensitization.

Tests performed in Part C serve as a control for the entire experiment. Their results, in conjunction with those of Parts A and B, suggest the following conclusions:

1. Leucocytes per se apparently have nothing to do with the production of autosensitization. Evidence for this assumption is the complete lack of antigenicity of a leucocyte suspension derived from a control and the failure of homologous or heterologous suspensions to increase the antigenicity of other tested agents. Such negative evidence, however, supports the contention of Cormia and Esplin that leucocytes are transporters of antigen. The 38% incidence of positive reactions to homologous leucocyte suspension in this study can best be explained on that basis.

2. Coagulase-negative Staph. albus per se is not antigenic to a person with autosensitization when tested intradermally. Incubation and conjugation with other substances are apparently required to produce detectible antigenic power.

3. Incubation of such a bacterium with substances derived from keratin or epidermal cells appears necessary to produce antigenicity.

The evidence of this study fails to support Cormia and Esplin's theory that a water-soluble substance derived from epidermal cells is the antigen responsible for autosensitization. Suspensions of heterologous and homologous skin scrapings from clinically normal areas proved to be weakly antigenic. The 62% incidence of positive reactions to skin scrapings taken adjacent to an area of inflammation can be

explained by the large amount of bacteria present. This amount is proportionately still greater at the site of primary inflammation. Positive skin-test reactions to suspensions of scrapings from this area should therefore be more frequent. The results in this study (75% incidence of positive reactions) support such reasoning.

If one assumes that an ordinarily nonpathogenic bacterium, growing on an acutely inflamed skin surface, is capable of becoming antigenic to the host, one must naturally consider the following questions:

1. Is such antigenicity demonstrable in the case of any inflammatory dermatosis?

2. If the answer to the first question is Yes, why is autosensitization not seen more frequently?

3. If the answer to the first question is No, why should such an antigenicity develop only in certain instances?

4. Is there some inherent allergic state or cutaneous hyperreactability responsible for autosensitization?

Results of this study leave such questions unanswered. They are mentioned for their stimulative value concerning further investigation of the problem.

CONCLUSIONS

Data are presented as evidence for the following conclusions:

1. The antigen responsible for cutaneous autosensitization is probably bacterial in origin.

2. The capacity for antigenicity is probably not limited to any one bacterial species; however, most antigenic species are ordinarily contaminants or the constituents of normal skin flora.

3. The incubation of these bacteria with substances derived from epidermal cells and keratin, as it occurs in vivo, appears necessary for the full formation of antigen.

4. Leucocytes per se have nothing to do with the production of antigen, but there is evidence to suggest that they may be antigen transporters from the site of formation to the reticuloendothelial system.

MALIGNANT GRANULOMA OF THE FACE

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FOR MANY years cases of destructive, usually fatal, idiopathic granulomatous ulcerating lesions of the facial structures have been encountered. These have been reported in the medical literature under a variety of titles.

Although not common, this entity must be of much more frequent occurrence than seems indicated by the number of cases hitherto reported. In this country, reviews, some of them extensive, have appeared in the otorhinolaryngologic literature only, and it is therefore probable that numerous instances of the syndrome have been overlooked or classified as some other condition by those not aware of its existence. It is my purpose at this time to present a review and two additional instances of this little-known but important entity.

REPORT OF CASES

CASE 1.—A 27-year-old white woman was admitted to the Los Angeles General Hospital in December, 1949, because of a persistent sore throat of six weeks' duration, which had not responded to intramuscular penicillin therapy. The patient had been in good general health, except for occasional epileptic seizures since infancy, controlled for the most part by phenobarbital and diphenylhydantoin (Dilantin) sodium and becoming less frequent after puberty. She had been married in 1947; her husband died in April, 1949, of adenocarcinoma of the thyroid with metastases. The rest of the history contained no unusual information.

Physical examination at entry disclosed a well-developed thin white woman who appeared in good general health. She was afebrile, with a pulse rate of 90, a respiratory rate of 20, and blood pressure of 115/70 mm. Hg. The relevant findings consisted of a small granulomatous lesion with a 1-cm. perforation on the soft palate near the base of the uvula. There was a midline area of erosion of the hard palate, covered by a tenacious gray exudate. The left side of the nose showed a swollen area on the anterior portion of the septum which bled easily on slight trauma, and there was obstruction of the air passage. No further positive physical findings were recorded, but one month later an enlargement of the spleen was detected.

Laboratory studies showed a blood hemoglobin concentration of 11.8 gm. per 100 cc., 4,600,000 erythrocytes and 6,500 leucocytes per cubic millimeter, with 73% neutrophiles, 18% lymphocytes, 7% monocytes, 1% basophiles and 1% eosinophiles. The serum albumin was 4.1 gm. and the globulin 3.3 gm. per 100 cc., the fasting blood sugar was 95 mg. per 100 cc., and the blood nonprotein nitrogen was 33 mg. per 100 cc. The serologic tests for syphilis, the complement fixation tests for coccidioidomycosis, and the serum agglutination tests for typhoid, paratyphoid, brucellosis, tularemia, and cold agglutinins all showed negative results. Urinalyses gave negative results. Examination of the cerebrospinal fluid disclosed no abnormal findings. Tuberculin, coccidiodin, histoplasmin, and Frei skin tests gave negative results. No acid-fast bacilli were found on nasal, palatal, and sputum smears and cultures. Cultures of the palatal lesion showed

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Candida albicans on two occasions, but no other fungi were ever found. Repeated aerobic and anaerobic bacterial cultures revealed Streptococcus viridans and Staphylococcus albus, coagulase negative, each time, and Staphylococcus aureus, coagulase positive, on one occasion.

Roentgenograms of the nasal bones showed that the septum and tip of the left nasal bone deviated to the right and that there was an opacity involving the left half of the nasal cavity. Further studies indicated a bilateral maxillary sinusitis and a bulging tumefaction of the posterior portion of the nasopharynx and epipharyngeal space. X-rays of the chest, skull, and hands gave negative results.

Repeated specimens for biopsy from the ulcerative lesion of the soft and hard palate were reported as "granulation tissue." A splenic smear examined for Histoplasma capsulatum showed

Fig. 1 (Case 1).—Small granulomatous mass on nasal septum and small ulcerating granuloma on palate, six months after onset of illness.

no organisms. Complement fixation tests and cultures for rhinoscleroma gave negative results. Biopsy specimen of an enlarged right inguinal lymph gland showed only benign hyperplasia.

Therapeutic agents used were penicillin, 300,000 units intramuscularly daily for prolonged periods up to a total of 25,000,000 units; streptomycin, 2 gm. daily, later reduced to 1 gm. daily, intramuscularly for approximately one month; aureomycin, 250 mg. orally every six hours for one month; saturated solution of potassium iodide orally, 10 to 30 minims (0.60 to 2 cc.), three times daily for two weeks, and antimony in the form of stibophen (Fuadin), 5 cc. intramuscularly three times weekly for three weeks.

There was no response to any of the medication mentioned above. The ulcerative and necrotic lesion occupying the posterior portion of the hard and soft palate in the midline became some-

what more extensive. Eating became more and more difficult because of pain. In May, 1950, there was an acute otitis media of the left ear, which subsided under penicillin therapy. The temperature, normal until then, began to show a daily rise to about 100 F. in early June, and from then on the patient was more or less constantly febrile, with the temperature rising daily up to 101 to 103 F., often dropping below 98 F. at night. There was progressive weight loss, amounting to about 60 lb. (27 kg.), weakness, and cachexia. Except for a terminal bronchopneumonia no other pathologic changes were noted during the hospital course. The patient died in August, approximately 10 months after the onset of her illness.

On postmortem examination, the enlarged spleen showed only engorgement and some increase in the germinal centers. The lungs exhibited evidence of a bronchopneumonia. Sections from the lesions of the pharynx and the soft palate showed only granulation tissue for the most part,

Fig. 2 (Case 2).—Unilateral enlargement of nose, six months after onset of illness.

although in one area the presence of masses of small cells supported by a delicate fibrous reticulum raised the question of mycosis fungoides or reticulum cell sarcoma.

CASE 2.—A 56-year-old Negro farm laborer came to the ear, nose, and throat clinic of the Kern General Hospital in July, 1951, complaining of swelling of the right side of the nose and face. He stated that this condition had been initiated by a fall on the nose six months earlier and that it had become progressively worse. The patient had been born in Texas, where he lived until coming to California. His general health had always been good, except for the usual childhood diseases. No further pertinent medical information was obtained.

The general physical examination showed a well-developed well-nourished man in no distress other than that incident to the facial involvement. The oral temperature was 99.2 F., and the blood pressure was 160/90 mm. Hg. There was definite enlargement of the right side of the nose, with a soft tissue mass in the right middle meatus. The left side of the face was swollen, with

marked edema of the eyelids, tenderness over the left antrum, and moderate proptosis of the left eye. No pathologic findings were elicited in the rest of the physical examination.

Laboratory studies showed a blood hemoglobin concentration of 11.8 gm. per 100 cc., 3,900,000 erythrocytes and 8,200 leucocytes per cubic millimeter, and a differential blood count of 31% lymphocytes, 66% neutrophiles, 2% monocytes, and 1% eosinophiles. The color index was 0.97. No sickling of the erythrocytes was seen. The blood serologic tests for syphilis gave negative responses. Urinalyses disclosed no abnormalities. Blood cultures gave negative results. On repeated attempts no fungi were grown from material taken from the involved area. Cultures from the nose revealed a hemolytic Streptococcus on one occasion and nonhemolytic Staphylococcus twice. The coccidioidin skin test gave a positive reaction, but the complement fixation and precipitin tests gave negative results.

The serum albumin was 3.1 gm. and the globulin 3.42 gm. per 100 cc. on Oct. 25. The circulating eosinophile count was 13 per cubic millimeter on Nov. 17 and 25 per cubic millimeter the following day.

X-rays taken on admission showed a probable fracture of the tip of the nasal bone, which was somewhat depressed. There was some callus formation around it. A specimen for biopsy was taken from the mass in the right nasal passage and reported as "polyp of the nasopharynx with acute inflammation." On Aug. 14 a Caldwell-Luc operation was performed on the left side and the maxillary sinus evacuated. Pathologic diagnosis of the tissue removed was granuloma of the maxillary sinus due to infection. Reexamination of the sinuses by x-rays then showed considerable thickening along the wall of the antrum, suggesting maxillary sinusitis, and there was much less clouding of the region as compared with what was seen on previous roentgenograms. A specimen for biopsy from the left nasal tumor was reported as "pyrogenic granuloma."

During his hospital stay the patient received the following medication: procaine penicillin, 300,000 units intramuscularly daily from Aug. 6 to Aug. 24; streptomycin, 250 mg. intramuscularly every six hours from Aug. 24 to Aug. 31; aureomycin, 250 mg. orally every four hours from Sept. 13 to Sept. 23; procaine penicillin again, 300,000 units intramuscularly daily from Sept. 23 to Dec. 2; chloramphenicol (Chloromycetin), 250 mg. orally every four hours from Dec. 2 until Dec. 20, and sulfadiazine, 1 gm. orally every four hours from Dec. 2 to Dec. 13. X-ray therapy was administered to the right eye, maxillary, frontal, and ethmoidal area in September, without evident improvement. Further x-ray therapy was contemplated, as was the administration of adrenal cortical hormone, but the patient died before these measures were carried out.

In addition to the usual supportive treatment, several transfusions were administered because of a progressive anemia. On Sept. 17, the hemoglobin concentration was 9.3 gm. per 100 cc., the erythrocyte count 3,350,000 per cubic millimeter and the leucocytes count 7,000 per cubic millimeter with 25% lymphocytes, 66% neutrophiles, 8% monocytes, and 1% eosinophiles. By Dec. 5, the hemoglobin level had dropped to 7.5 gm. per 100 cc., the erythrocyte count was 3,160,000 per cubic millimeter and the leucocyte count 4,200 per cubic millimeter, with 29% lymphocytes, 65% neutrophiles, and 6% monocytes.

During the first week of his hospital course the patient's temperature remained slightly elevated, under 100 F. One week after admission the temperature rose to 103 F., and thereafter it ran a septic course. From the time he was first seen, the patient became progressively worse, with increasing weakness and emaciation. The swelling of the left cheek and the periorbital area decreased, and the proptosis of the left eye did not change appreciably, but the destructive process of the nose became very extensive. The patient died Dec. 22, about 10 months after the onset of his illness. No postmortem examination was performed.

REVIEW OF THE LITERATURE

In 1896 McBride [1] presented a case of rapid destruction of the nose and face before the Laryngological Society of London. His patient was a 28-year-old white

1. McBride, P.: Case of Rapid Destruction of the Nose and Face, J. Laryng. & Otol. **12**:64-66, 1897.

Fig. 3 (Case 2).—Mass within nasal cavity, 10 months after onset of illness.

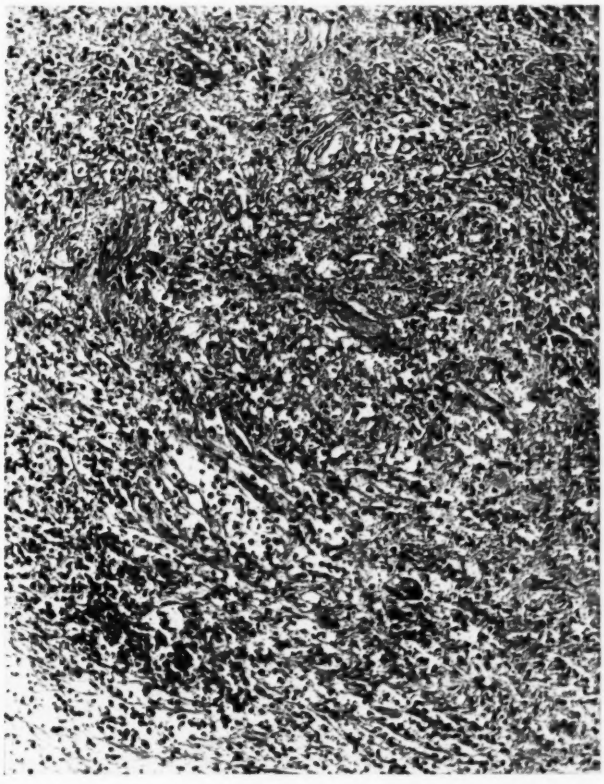

Fig. 4 (Case 1).—Low-power photomicrograph, showing the banal granulomatous nature of the palatal lesion.

man who gave a history of having scratched the inner surface of the ala nasi. One week later swelling of the nose was noted. When he was seen the following month there was an ulcerated lesion at the site of the injury. From this trivial onset a destructive process continued which led to the patient's death in nine months. P. G. Unna saw the patient at one time and suggested that the possibilities of glanders and syphilis be investigated. Agar cultures and guinea-pig inoculations produced no evidence of glanders, and mercurial inunctions caused no improvement.

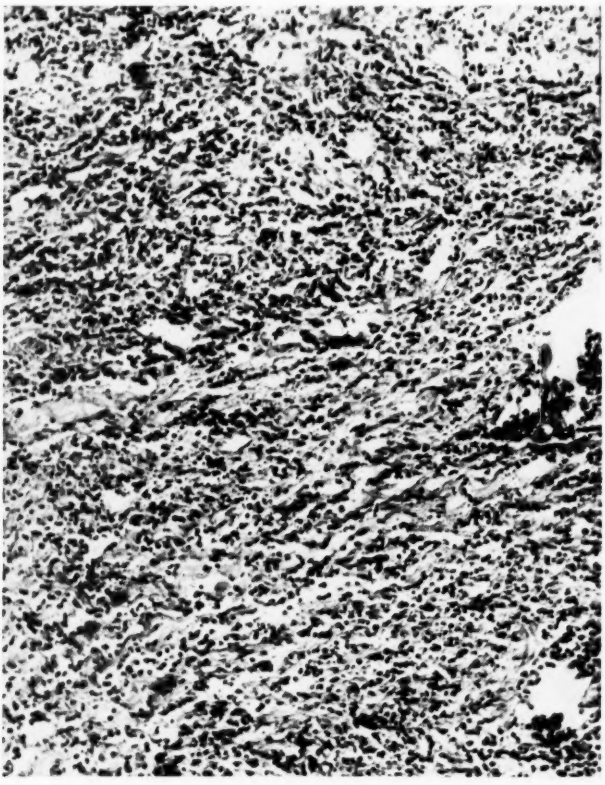

Fig. 5 (Case 2).—Low-power photomicrograph of nasal lesion, showing similar granulation tissue.

Since then there have been similar reports. In 1921 Woods [2] described two cases of "malignant granuloma of the nose," and in 1925 M'Arthur,[3] under the same title, presented an instance of the entity seen in Australia. Arrowsmith's [4] case of a 38-year-old Italian-born man, although presented as gangosa, may be the first American report. The patient's death after a two-year illness during which no

2. Woods, R.: Malignant Granuloma of the Nose, Brit. M. J. **2**:65-66 (July 16) 1921.

3. M'Arthur, G. A. D., and Dew, H. R.: Malignant Granuloma of the Nose, J. Laryng. & Otol. **40**:378-380 (June) 1925.

4. Arrowsmith, H.: Gangosa, Laryngoscope **31**:843-846 (Nov.) 1921.

spirochetes were demonstrated, no lesions developed elsewhere, and in which there was no response to antisyphilitic therapy makes the diagnosis of gangosa, which today is considered a manifestation of yaws, rather improbable. However, what is usually accepted as the first American report is that of Wood,[5] "a case of mutilating granuloma of the nose and face with fatal ending." The patient was a 32-year-old woman with the characteristic history of a watery nasal discharge, followed by swelling and soreness of the tip of the nose. Examination showed a necrotic mass filling the anterior portions of both nasal fossa. Only various pyogenic organisms were found on culture. Antisyphilitic therapy was of no avail. Death was due to "general exhaustion."

An exhaustive review of the subject appeared in 1933 (Stewart[6]), in which the author accepted the cases of McBride,[1] Woods,[2] M'Arthur,[3] Wood,[5] and Chatellier[7] as falling into a group he designated "progressive lethal granulomatous ulceration of the nose." To these he added five of his own. Reports in the German literature are by Berendes,[8] cited by Joisten,[9] who collected 16 cases from the German literature, 9 from the English, and 1 each from the Japanese, French, and Italian literature. To these, Joisten[9] added two of his own. Additional reports in German publications are by Bayer,[10] Schütz,[11] Voss,[12] and Wegener.[13] A Scandinavian report is by Rasmussen,[14] who reviewed the subject and added two additional cases, introducing the title "osteomyelitis necroticans faciei."

In American publications, Lierle[15] reported an instance in a 22-year-old woman. Hoover[16] reviewed the subject, adding four cases of his own occurring in men plus an atypical instance in a woman who survived, and he chose the title "granulomatous ulcer of the nose and face of unknown cause." Isbell[17] accepted this designation in

5. Wood, G. B.: A Case of Mutilating Granuloma of the Nose and Face with Fatal Ending, Tr. Am. Laryng. A. **53**:62-71, 1931.

6. Stewart, J. P.: Progressive Lethal Granulomatous Ulceration of the Nose, J. Laryng. & Otol. **48**:657-701 (Oct.) 1933.

7. Chatellier, L.: Sacro-lupus pernio mutilant et mortel, Ann. dermat. et syph. **10**:1213-1230 (Nov.) 1929.

8. Berendes, J.: Granuloma gangränescens, München med. Wchnschr. **81**:2005-2006 (Dec. 27) 1934.

9. Joisten, E.: Zwei ätiologisch unklare Fälle von gangräneszierende Entzündung der Nase und des Oberkiefers, Ztschr. Hals- Nasen- u. Ohrenh. **41**:105-128 (Sept. 16) 1936.

10. Bayer, H. G. A.: Ätiologisch unklare, gangräneszierende Erkrankungen des Nasenskeletts, Hals-, Nasen- u. Ohrenarzt (Pt. 1) **28**:83-94 (April) 1937.

11. Schütz, W.: Verschiedene Formen von Gangrän der Nase und Nasennebenhöhlen, Ztschr. Hals- Nasen- u. Ohrenh. **44**:244-250, 1938.

12. Voss, O.: Progressives malignes Granulom der Luftwege, Ztschr. Laryng. Rhin. Otol. **25**:122-130, 1934.

13. Wegener, F.: Über eine eigenartige rhinogene Granulomatose mit besonderer Beteiligung des Arterien-system und der Nieren, Beitr. path. Anat. **102**:36-68, 1939.

14. Rasmussen, H.: Osteomyelitis necroticans faciei, Acta oto-laryng. **33**:254-261 (May-June) 1945.

15. Lierle, D. M.: Chronic Infectious Granuloma of the Nose, Arch. Otolaryng. **36**:940-943 (Dec.) 1942.

16. Hoover, W. B.: Granulomatous Ulcer of the Nose and Face: Of Unknown Cause, Usually Progressive, Gangrenous and Fatal, Arch. Otolaryng. **34**:865-879 (Nov.) 1941.

17. Isbell, D.: Chronic Granulomatous Ulcer of the Nose of Unknown Cause, Ann. Otol. Rhin. & Laryng. **52**:501-506 (June) 1943.

adding an additional case report. More recently, Williams [18] published a survey of the subject, adopting with modifications the title used by Stewart.[6] In a paper on nonmalignant granulomatous lesions of the oral and nasal cavities Havens [19] makes mention of Williams' [18] cases. In recent years further reports have appeared, particularly from Williams and his co-workers in this country, as well as reports from Britain.

The reviews by Stewart,[6] Hoover,[16] and Williams [18] are particularly recommended.

The precise number of reported cases which can be accepted is impossible to ascertain, since clear-cut criteria are difficult to assign, and since, as with any idiopathic condition, the painstaking exclusion of all other possible causes of similar conditions, in this instance, of destructive processes of the face, must have been achieved by intensive clinical and laboratory studies. Some of the case reports do not provide information sufficient to rule out other conditions, such as an unclassified carcinoma or sarcoma.[20] There are other reports of destructive granulomas, both with and without involvement elsewhere, which have been carefully studied, but which do not seem to fit into any known category. Some of these may fall into this group.[21]

Increasing awareness of specific causes decreases the number of cases acceptable as idiopathic. Thus, in reviewing older reports, such destructive facial granulomas considered idiopathic at the time of their publication, in the light of present knowledge seem to be attributable to more specific causes. Fordyce [22] reported a "case of undetermined tropical ulcer" in a native of Central America which strongly suggests the possibility of American leishmaniasis. A case of Henry Macnaughton Jones [23] was considered by the discussants as factitial, and the author had himself entertained that possibility. Similarly, Nabarro's [24] report of an 11-year-old girl whose condition was cured in 14 days by the oral administration of extract of the common

18. Williams, H. L.: Lethal Granulomatous Ulceration Involving the Midline Facial Tissues, Ann. Otol. Rhin. & Laryng. **58**:1013-1054 (Dec.) 1949.

19. Havens, F. Z.: Nonmalignant Granulomatous Lesions of the Nasal and Oral Cavities, Tr. Am. Acad. Ophth. **54**:235-244 (Jan.-Feb.) 1950.

20. (*a*) Hall, I. S.: Malignant Granuloma of the Hard Palate, J. Laryng. & Otol. **48**:777 (Nov.) 1933. (*b*) Kanas, S.: Ein Fall von "malignem Granulom" des Rachens: (Atypisches Lymphosarkom), Acta oto-laryng. **23**:429-444, 1936; abstracted, J. Laryng. & Otol. **51**:613 (Sept.) 1936. (*c*) Meara, R. H.: Chronic Granuloma of the Nose: For Diagnosis, Brit. J. Dermat. **62**:271-272 (June) 1950. (*d*) Shebesta, E. M.: Gangrene of Face Produced by Lymphosarcoma, Radiology **29**:33-36 (July) 1937.

21. (*a*) Dennie, C. C.; Hamilton, T. R., and Quinn, H. F.: Massive Destruction of the Face, Arch. Dermat. & Syph. **42**:1040-1045 (Dec.) 1940. (*b*) Padgett, E. C.: Osteomyelitis of the Jaws: Analysis of 59 Patients, Surgery **8**:821-831 (Nov.) 1940. (*c*) Lewis, G. M.: A Case for Diagnosis: Granuloma of the Nose? Tertiary Syphilid, Treatment Resistant? A. M. A. Arch. Dermat. & Syph. **65**:107 (Jan.) 1952.

22. Fordyce, J. A.: A Case of Undetermined Tropical Ulcer Involving the Nose, Pharynx, and Larynx, with Histological Findings, J. Cutan. Dis. **44**:1, 1906.

23. Jones, H. M.: Esthiomenic Menstrual Ulcer of the Nose, J. Laryng. & Otol. **12**:207-210, 1897.

24. Nabarro, D.: An Obscure Case of Ulceration of the Nose in a Child Simulating an Epithelioma, Brit. J. Surg. **1**:576, 1914.

alder (sic) may also have been factitial. Occasionally, other rare occurrences may lead to somewhat similar clinical pictures, as in the case of a foreign body granuloma of the nose due to gauze left following an injury.[25]

Allowing a liberal interpretation of reported instances, not more than 70 have appeared. In these, male patients predominate by a ratio of about 10 to 1. The youngest reported patient was 11, two were over 60, but the bulk were between 20 and 50 years of age. Most of the reports are of British, American, and German cases, with other reports coming from Australia, Denmark, Italy, Japan, France,[26] and Russia.[27]

ETIOLOGY

The cause of this condition is as yet completely uncertain. Dempsey,[28] in 1933, defined it as a tumor of unknown etiology, due to no visible organisms, made up of granulation tissue, and malignant in its behavior. Sneddon and Colquhoun[29] suggested that the granulomatous overgrowth is a nonspecific reaction to a staphylococcal infection and pointed to the common pyogenic granuloma as a good example of exuberant granulation tissue stimulated by such infection. In their case, a penicillin-resistant Staphylococcus was repeatedly isolated, and the infection was controlled by chloramphenicol therapy. Pfister[30] also found a penicillin-resistant Staphylococcus in his case and reported cure following the use of aureomycin orally and bacitracin ointment topically. Although streptococci and staphylococci have been commonly found, nevertheless, control of these organisms by antibiotics has usually failed to affect the course of the disease. Hoover[16] suggested that virus studies be done. To date, this has not been accomplished, so that the possibility of a virus causation remains.

The possible relationship to the so-called collagen diseases has been the subject of much recent discussion. Williams[18] developed at length the view that the occurrence of granulomatous inflammation without an adequate stimulus can be considered a type of allergy, resting on a disorder of the secretion of 17-hydroxy-11-dehydroxycorticosterone. Moore, Williams, and others[31] reported the case of a 50-year-old woman in whom an idiopathic granuloma of the nose developed which secondarily involved the nasopharyngeal and laryngeal regions. A rheumatoid arthritis developed synchronously with the laryngeal involvement, and skin lesions resembling those of disseminate lupus erythematosus developed on the elbows, hands,

25. Pearlman, S. J., and Pilot, I.: Foreign Body Granuloma of the Nose, Laryngoscope **33**:854-856 (Nov.) 1923.

26. Tischnenko, A.; Kroitschik, A., and Kusnetz, M.: Étude clinique du granuloma gangrænescens, Ann. dermat. et syph. **7**:763-772 (Aug.) 1936; abstracted, Urol. & Cutan. Rev. **41**:290-291 (April) 1937.

27. Derischanoff, S.: Granuloma gangraenescens, Arch. Dermat. u. Syph. **164**:756-760, 1932.

28. Dempsey, P.: Nasal Granulomata, Brit. M. J. **2**:194-196 (July 29) 1933.

29. Sneddon, I. B., and Colquhoun, J.: Granulomatous Ulcer of the Nose Treated with Chloramphenicol, Brit. M. J. **1**:298-300 (Feb. 9) 1952.

30. Pfister, R. L.: Granulomatous Ulcer of the Face: Report of a Case, Laryngoscope **61**:937-941 (Sept.) 1951.

31. Moore, P. M.; Beard, E. E.; Thoburn, T. W., and Williams, H. L.: Idiopathic (Lethal) Granuloma of the Midline Facial Tissues Treated with Cortisone: Report of a Case, Laryngoscope **61**:320-331 (April) 1951.

and feet. This case illustrates their concept that idiopathic lethal granuloma of the facial tissues is an instance of localized hyperimmunity which may be grouped with the other collagen diseases. In several other instances patients have had postmortem findings in other organs characteristic of periarteritis nodosa (Wegener,[13] Weinberg,[32] and Williams [18]).

Woodburn and Harris [33] reported postmortem findings on two of six patients they had observed. In one, the internal organs were entirely normal; in the other, there was found chronic glomerulonephritis, acute necrotizing arteritis involving the kidneys, skeletal muscles, lungs, esophagus, and small intestine, nonspecific granulomatous ulcerations of the nose, nasopharynx, pharynx, and larynx, acute pericarditis, and a terminal bronchopneumonia. The clinical course in this patient, a 31-year-old white man, had begun with a nasal lesion and, at the same time, a generalized and recurrent papular skin eruption, with ulceration of some of the skin lesions. Thus, this may well have been an instance of polyarteritis nodosa in which the nasal condition was a manifestation of the systemic disorder. McCart [34] reported two somewhat similar instances.

Friedman [35] summarized the association of granulomatous lesions in various organs with polyarteritis nodosa, suggesting that in some cases hypersensitivity due to chronic infection may be the underlying cause leading to the terminal development of polyarteritis nodosa, while in others the granulomatous lesion in the nose and sinuses may possibly represent a local manifestation of the disease itself. Both of these relationships seem possible, as demonstrated in the examples cited. However, in the two cases dealt with in this report no evidence of systemic involvement existed, and the same is true for most of the other reported cases.

In his early paper Woods [2] posed the question, "If we can have a malignant epithelioma, why not a malignant granuloma?" which question seems as pertinent now as it did 30 years ago.

HISTOLOGIC OBSERVATIONS

With considerable uniformity, the microscopic findings have been categorized as those of chronic inflammation. Material from the case of McBride,[1] probably the first in the literature, was studied by Dr. Muir, pathologist to the Royal Infirmary. He was of the opinion that the disease did not correspond to any type with which he was familiar. The sections showed marked endarteritis, suggesting tertiary syphilis to some. Wood [5] submitted sections to Dr. James Ewing and Dr. Frederick Weidman. Dr. Ewing stated that "unless we have an entirely new disease we are thrown back on syphilis or mycosia fungoides." Dr. Weidman was of the opinion that the condition was not in any true sense a neoplasm, that it was not syphilis, tuberculosis, or any disease that he knew of, although it probably belonged to the so-called granulomas.

32. Weinberg, T.: Periarteritis Nodosa in Granuloma of Unknown Etiology: Report of Two Cases, Am. J. Clin. Path. **16**:784-791 (Dec.) 1946.

33. Woodburn, C. C., and Harris, H. E.: Idiopathic Lethal Granulomatous Ulceration of the Nose and Face, Cleveland Clin. Quart. **18**:165-178 (July) 1951.

34. McCart, H.: Malignant Granuloma of the Nose, Canad. M. A. J. **63**:357-361 (Oct.) 1950.

35. Friedmann, I.: Malignant Granuloma of the Nose, Brit. M. J. **1**:491 (March 1) 1952.

Stewart [6] summarized the pathologic findings as a chronic inflammatory process, with proliferation of endothelial cells, lymphocytes, and plasma cells, and formation of granulation tissue, at first cellular, but later becoming fibrous. He stated that material from early cases showed principally round-cell infiltration, with necrosis of the epithelium. As the disease progressed, fibrous tissue was laid down, fairly loosely just beneath the surface and more densely in the deeper parts, with small round-cell infiltrate still present among the fibrous tissue. The blood vessels were proliferating in the early stages and later had enormous thickening of their walls and endarteritis with hyaline changes. Other descriptions of the histologic findings were "chronic inflammatory changes" (Isbell [17]), "inflammatory tissue with many plasma cells" (Lewy [36]), "chronic infectious granuloma" (Lierle [15]), and "simple granulation tissue" (Rasmussen [11]).

Woodburn and Harris,[33] who reported six cases encountered over a 15-year period, submitted sections to various pathologists, who were unable to agree on a definite diagnosis, the opinions varying between granulomatous inflammation of an unusual type and neoplastic disease.

DIFFERENTIAL DIAGNOSIS

These cases, while varying in many of their aspects from one another, still afford sufficient points of similarity to justify their being grouped together. The prime characteristics of these granulomas are their site of origin in the nose or palate, their usually ineluctable progress, with ulceration and destruction of the central facial structures, and their evidently idiopathic nature.

Essentially the diagnosis is arrived at reluctantly, after the exclusion of other causes of destructive facial processes, through clinical and laboratory studies, and/or failure of response to therapeutic agents effective in other conditions. The commonest conditions which enter into the differential diagnosis are tuberculosis, syphilis, and carcinoma. In cases of destructive lesions of the face considered to be treatment-resistant tertiary syphilids, particularly in view of negative results of serologic tests, a granuloma of this type must certainly be considered.[21c] With the efficient antisyphilitic drugs and sensitive serologic tests now available, it would seem far less likely to encounter the combination of treatment-resistance and absence of a positive serologic reaction for syphilis.

The following list is offered as requiring more or less serious consideration before any given case can be termed idiopathic: malignant processes including carcinoma, sarcoma, and the lymphoblastomas, especially mycosis fungoides [37]; the deep mycoses including European blastomycosis, American blastomycosis, coccidioidomycosis, sporotrichosis, and rhinosporidiosis; other specific infectious granulomas including syphilis,[38] yaws, tuberculosis, leprosy, tularemia, glanders,[39] leishmaniasis, granuloma venereum, and rhinoscleroma; myiasis; factitial lesions;

36. Lewy, A.: A Case of Gangrenous Osteomyelitis of the Paranasal Sinuses, Arch. Otolaryng. **27**:91-94 (Jan.) 1938.

37. Behr, E.: Ulceration of Nose and Face Caused by Mycosis Fungoides, Nederl. tijdschr. geneesk. **78**:2197-2207 (May 19) 1934; abstracted, Am. J. Dis. Child. **51**:209 (Jan.) 1936.

38. Cole, H. N.; Driver, J. R., and Freeman, H. E.: Syphilis of the Center of the Face, Arch. Dermat. & Syph. **43**:943-948 (June) 1941.

39. Sobol, I.: A Case of Chronic Nasal Glanders, Acta oto-laryng. **18**:500-509, 1933.

periarteritis nodosa; trophic postencephalitic ulcers; sarcoidosis; agranulocytosis; Meleney's synergistic gangrene,[40] and osteomyelitis.[21b] Williams and Hochfilzer [41] pointed out that unless specific organisms are found in the lesion, idiopathic and infectious granulomas frequently cannot be distinguished.

CLINICAL COURSE

Stewart's [6] division of the clinical course into three stages appears applicable to most instances of the disorder.

The first or prodromal stage may last from a few months to several years and is characterized by a feeling of discomfort or stuffiness in the nose, usually with a watery or serosanguinous discharge.

After this insidious and seemingly innocuous onset, there is the period of active disease. The symptoms become progressively worse, with definite nasal obstruction in almost every case. There is a fetid odor to the nasal discharge, and the nose is filled with adherent often gelatinous crusts which on removal reveal areas of ulceration. The tip of the nose may show reddening and induration. As the ulcerating granulomatous area spreads perforations of the septum, palate, and later through the soft parts of the face adjacent to the nose appear. Minor hemorrhages were frequent. The temperature may remain normal for a long time, but ultimately an irregular fever, imperfectly controlled by administration of antibiotics, is more often found. The usual painlessness of the lesions was stressed by Voss [12] in his report of two cases, including one which showed an unusual expansion to the larynx, trachea, and bronchi. Awkwardness in swallowing may be the chief complaint, but occasionally there may be severe pain. There is no characteristic blood picture at any time. A mild leucocytosis or even a mild leucopenia may occur, but the proportion of polymorphonuclear leucocytes remains relatively normal, and agranulocytosis is never found.

During the third or terminal phase extensive mutilating destruction of the center of the face is usual. As swallowing becomes increasingly difficult, the nutritional status deteriorates. Repeated hemorrhages may be difficult to control. The temperature becomes more septic in character, and progressive cachexia ensues. Finally, after a course of usually 6 to 36 months in duration, the patient dies, with a terminal pneumonia, cachexia, or hemorrhage as the immediate cause of death.

The large majority of cases have terminated fatally. There are occasional reports of recovery in instances which have seemingly conformed to the criteria for this disorder. Hoover,[16] in recording such a case, suggested simply that the defense mechanism of the body may prove capable of overcoming the unknown causative factor in an occasional patient.

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40. Meleney, F. L.: A Differential Diagnosis Between Certain Types of Infectious Gangrene of the Skin, with Particular Reference to Hæmolytic Streptococcus Gangrene and Bacterial Synergistic Gangrene, Surg., Gynec. & Obst. **56**:847, 1933.

41. Williams, H. L., and Hochfilzer, J. J.: Effect of Cortisone on Idiopathic Granuloma of the Midline Tissues of the Face, Ann. Otol. Rhin. & Laryng. **59**:518-530 (June) 1950.

RESPONSE TO THERAPY

A wide range of treatment measures have been employed, with generally disappointing results. Where remissions have been obtained, it is difficult to ascribe them clearly to the therapy employed, and other patients treated by the same means have failed to improve. Thus, while x-ray and radium therapy seemed to help for a time, according to some (M'Arthur,[3] Woods,[2] Heinermann [42]), others felt that the condition of their patients was made worse by such treatment (Hoover,[16] Lewy [36]). In those cases where they have been used, the arsphenamines, mercurials, iodides, and antimony preparations have all failed to stop the progress of the disease.

Surgical intervention has likewise not been beneficial. Indeed, Isbell [17] recommended avoiding the trauma incidental to mechanical cleansing.

Curtis [43] (in discussion of Havens [19]) called attention to certain granulomas which respond to nascent oxygen therapy, as with zinc peroxide paste. If an anaerobic or microaerophilic organism is found, such treatment may be indicated.

Williams' [18] estimation that the antibiotics do not affect the ultimate course but may aid temporarily by the elimination of secondary invading organisms is born out by the experience reported in this paper with penicillin, streptomycin, aureomycin, and chloramphenicol. The sulfonamides have done no more (Hoover,[16] Rasmussen [14]). However, as previously mentioned, Sneddon and Colquhoun [29] reported a case in which they believed the condition to be caused by a penicillin-resistant Staphylococcus and were able to control the disease process by the administration of chloramphenicol. Pfister [30] felt that a penicillin-resistant S. aureus was the cause of the disease in a case he reported, and he obtained healing with the use of aureomycin orally and a bacitracin ointment locally. Hargrove [44] reported a case in which penicillin appeared to control the spread of the lesion, but the patient died of pneumonia.

Recent therapeutic attempts, especially by Williams [18] and his co-workers, have included the use of cortisone and corticotropin (ACTH).

Williams [18] administered 100 cc. of an extract of adrenal cortex to one of his patients, and noted that the patient seemed to show a marked improvement after this injection, but died the following afternoon .

Williams and Hochfilzer [41] later reported temporary improvement in another instance following administration of cortisone, but stated that although healing was observed, the progress was very slow and was not sustained. A patient recently under observation at the Los Angeles General Hospital received a daily intravenous administration of 25 mg. of corticotropin in 1,000 cc. of 5% dextrose solution, with improvement of appetite and a general feeling of well-being. However, a rise of the blood pressure to 270/140 mm. Hg. and evidence of congestive failure made it impossible to continue treatment. There was little change in the facial lesion. Woodburn and Harris [33] obtained immediate amelioration and apparent cure in one patient with the use of cortisone, but in a recurrence several months later the patient failed to respond in a similar fashion. Another patient obtained a partial remission with corticotropin. These authors felt that although these drugs appeared

42. Heinermann, E.: Das Granuloma gangraenescens und seine Behandlung mit Vitamin C und Röntgenstrahlen, Munchen med. Wchnschr. **85**:2023-2024 (Dec. 30) 1938; abstracted, Radiology **33**:254 (July-Dec.) 1939.

43. Curtis, A. C., in discussion of Havens.[19]

44. Hargrove, S. W. G.; Fodden, J. H., and Rhodes, A. J.: Malignant Granuloma of the Nose, Lancet **2**:596-599 (Oct. 26) 1946.

to offer the only effective available remedy, they probably do not result in cure, and that the treatment remains empirical. They viewed the prognosis with extreme pessimism.

SUMMARY

Two cases of malignant granuloma of the face are presented and the syndrome reviewed.

Malignant granuloma of the face may be defined as an idiopathic usually lethal tumor of granulation tissue arising in the nose or palate. It is probably far more common than is indicated by the paucity of published reports and should be considered early in the study of any obscure destructive process of the face.

The cause remains unknown. A specific organism has not been demonstrated. Some have considered malignant granuloma to represent a failure of the normal defense mechanism against common organisms such as staphylococci or streptococci, or a type of allergy in the same general category as polyarteritis nodosa. While some instances appear to be part of the polyarteritis nodosa syndrome and in others the facial lesion may have initiated such a process, in most there has been no such relationship.

The clinical course is characterized by a slow onset, followed by gradual enlargement of a destructive and ulcerating granulomatous tumor, with only minor and temporary remissions. The site of origin is either the interior of the nose or the palate, with extension limited to the adjacent structures, the paranasal sinuses, the anterior oropharynx, and the soft parts of the center of the face. Involvement of distant organs is mentioned only in reports in which the facial lesions appeared to be part of a polyarteritis nodosa syndrome. The patient's general condition remains surprisingly good until late in the course of the disease.

The more common causes of such a mutilating process may be quite readily excluded by biopsy, serologic tests for syphilis, blood cell counts, microscopic examination, and cultures for organisms. Ordinarily, only staphylococci and/or streptococci can be demonstrated. Histologic findings, while not pathognomonic, have been consistent in that only granulation tissue has been found. Distant metastases composed of similar tissue are conspicuously absent, although such may have been present in a case reported by Hall.[20a] Once these basic studies have failed to elicit significant positive findings, malignant granuloma warrants consideration as a working diagnosis.

As in pemphigus, the outcome is usually fatal, with an occasional and unpredictable cure bearing no consistent relationship to therapy. However, since recoveries have been reported, therapeutic attempts are certainly indicated. At present, it would appear that treatment should include administration of antibiotics, at least for the control of secondary infections, supportive measures with transfusions as indicated by the patient's general condition, possibly x-ray therapy, and further trials of corticotropin (ACTH) or cortisone. Employment of these measures should not be delayed pending exclusion of every remote diagnostic possibility.

As to the nomenclature, since the cause remains unknown, the selection of a title must be on a descriptive basis. "Malignant granuloma" has historical precedence and seems otherwise very acceptable.

2026 17th St.

Clinical Notes, New Instruments and Techniques

EFOCAINE IN CONTROL OF PRURITUS

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My interest in the use of procaine to control pruritus has extended over a long period. Recently my colleagues and I [1] reported on the use of intravenous procaine hydrochloride and are now studying the effects of orally administered procaine-ascorbic-acid combination. This present report deals with the use of a new local anesthetic solution, Efocaine. This product is a combination of procaine base and butyl *p*-aminobenzoate, which are insoluble in water, but are soluble in the aqueous miscible nontoxic organic solvents, propylene glycol and polyethylene glycol. This solution is at saturation limits, so that when injected into the tissue the contact with aqueous tissue fluids causes the complete precipitation of the active ingredients. The inert solvents are rapidly absorbed and excreted, leaving a microcrystalline drug repository along the lines of injection. The anesthetic depot is slowly absorbed, its effects continuing for a prolonged period. The mechanism of action of this drug is based upon the creation of an in vivo depot of the anesthetic bases. Efocaine has been reported [2] to produce a high degree of pain relief following major and minor surgery; toxic reactions, both local and general, were lacking. These studies reported a prolonged anesthetic effect persisting as long as two weeks.

Local anesthesia as a means to combat pruritus has been attempted since the introduction of injectible anesthetic bases. The rationale is based on the interruption of the pain-spasm cycle by the agent blocking both afferent and efferent stimuli. Aqueous solutions of local anesthetics do not produce an effect for a sufficient period of time. Oil solutions of the anesthetics were later introduced in order to prolong the duration of anesthesia.[3] The work of Kelly [4] and Duncan [5] established the fact that the oil solution produced little or no increase in the effective anesthetic duration. Brown,[6] Emery,[7] and Freyberg [8] confirmed this opinion. Because the oils

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From the Department of Dermatology, Western Pennsylvania Hospital, L. G. Beinhauer, M.D., Chief.

1. Beinhauer, L. G.; Thomas, G. J., and Perrin, S. R.: Intravenous Use of Procaine Hydrochloride in Control of Pruritus, A. M. A. Arch. Dermat. & Syph. **65**:39, 1952.

2. Ansbro, F. P.; Iason, A. H.; Shaftel, H. E.; Halpern, A.; Latteri, E., and Bodell, B.: The Development of Efocaine: A New Approach to Prolonged Local Anesthesia, Anesthesiology **13**:306, 1952. Iason, A. H., and Shaftel, H. E.: A New Approach to the Problem of Postoperative Pain, Am. J. Surg. **83**:549, 1952. Deaton, W. R., Jr., and Bradshaw, H. H.: A Long-Lasting Local Anesthetic Solution: Use in Thoracic Surgery, Am. Surgeon **18**:616, 1952. Tucker, C. C.: The Control of Postoperative Pain in Ano-Rectal Surgery, J. Kansas M. Soc. **53**:230, 1952. Gross, J. M., and Shaftel, H. E.: The Role of Efocaine in Anorectal Anesthesia and Analgesia, New York J. Med. **52**:1413, 1952.

3. Yeomans, F. C.; Gorsch, R. V., and Mathesheimer, J. L.: Benacol in Treatment of Pruritus Ani: Preliminary Report, M. Rec. **127**:19, 1928.

4. Kelly, M.: Failure of Oil-Soluble Anesthetics to Give Prolonged Analgesia, Lancet **1**:710, 1947.

5. Duncan, D., and Jarvis, W. H.: A Comparison of the Actions on Nerve Fibers of Certain Anesthetic Mixtures and Substances in Oil, Anesthesiology **4**:465, 1943.

6. Brown, W. E.; Wilder, V. M., and Schwartz, P.: A Study of Oils Used for Intramuscular Injections: Study of Physical, Chemical, and Biologic Factors, J. Lab. & Clin. Med. **29**:259, 1944.

7. Emery, F. E., and Matthews, C. S.: Note on Cysts and Abscesses Induced in Rat by Injection of Oils, J. Lab. & Clin. Med. **28**:1795, 1943.

8. Freyberg, R. H.: Gold Salts in Treatment of Chronic Arthritis: Metabolic and Clinical Studies, Proc. Staff Meet., Mayo Clin. **17**:534, 1942.

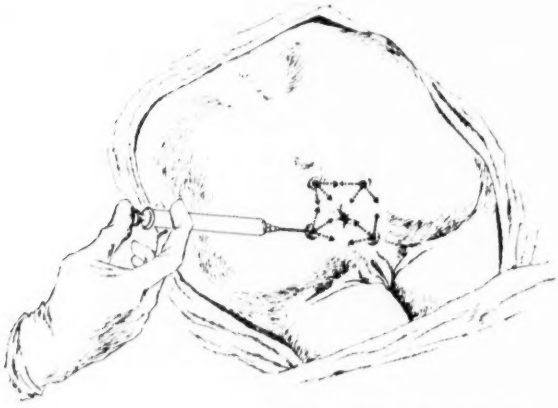

Fig. 1.—About 2 to 3 cc. is injected into each quadrant.

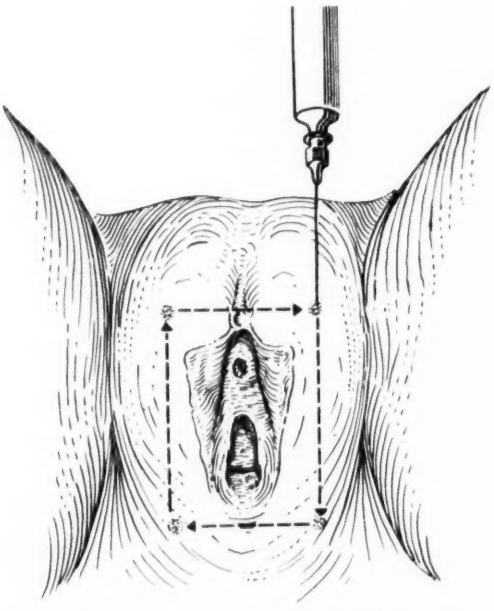

Fig. 2.—The injection should be made into the deeper tissues, using between 5 and 10 cc. for the complete injection.

are immiscible with body fluids they may become encapsulated to form cysts which may terminate in abscesses, sloughs, foreign-body granulomas, and local tissue-reaction requiring surgical intervention.[9]

Histopathological investigation[10] revealed Efocaine to be free of foreign-body reactions and inflammatory-tissue responses. No gross tissue destruction or permanent necrotic changes were observed. No neurodegeneration was noted.

MATERIAL AND METHODS

Forty-two patients with pruritic dermatoses were selected for this study. These patients had previously had recognized therapy, such as x-ray, topical applications, oil-anesthetic injections, and alcohol injections, without relief. Each patient was treated by local injection, and in order to simplify the mechanical procedure of injection the accompanying figures are submitted for the various areas treated.

Fig. 3.—About 2 to 5 cc. is used in the deeper subcutaneous tissue.

The following precautions were observed when carrying out the injections:

1. Pooling of the drug was carefully avoided, as well as superficial injection. Since a solid microcrystalline depot results, pooling produces a bolus of material which predisposes toward sloughing, while superficial injection causes erosion of the tissue by the solid anesthetics. The injection should be made as a series of fine lines about ¼ to ½ in. (0.6 to 1 cm.) deep, using a fine bore needle. Intradermal introduction of the drug produces a necrotic reaction and must be avoided in all instances.

2. A local stinging pain results when Efocaine is injected, due to the hypertonic properties of the solvent, but is of no clinical consequence. It may be minimized by the use of a skin wheal (with aqueous procaine hydrochloride) and by injection of a small amount of this same aqueous solution into the immediate subjacent tissue before the injection of Efocaine.

Pruritus Ani (Fig. 1).—The skin is carefully cleansed, and a skin wheal is raised with aqueous procaine hydrochloride at the "four quadrants of the anal clock" to minimize any local burning

9. Smith, T. E.: Relief of Pain Following Anorectal Surgery, South. M. J. **36**:650, 1943.

10. Weinberg, T.: Personal communication to the author.

or pain from the injection. After a few minutes, a 3-in. (7.6 cm.) 20- or 22-gauge needle is inserted through the skin wheal into the deeper subcutaneous tissue (about ¼ to ½ in. [0.6 to 1 cm.] deep) and directed toward the anal verge, and the Efocaine is injected as the needle is withdrawn. The needle is then withdrawn almost to the skin surface and reinserted in another direction. This fanwise procedure is repeated in order to create a series of fine lines for each quadrant. A dose of 2 to 3 cc. of the drug should be injected into each quadrant, with a total dose of 10 cc. for the complete perianal infiltration.

Pruritus Vulvae (Fig. 2).—As noted in the drawing, four wheals are raised. Injection of Efocaine is carried out, as described previously, into the deeper tissues. Local burning may be encountered in this area. The average dose is 10 cc. for complete infiltration.

Localized Pruritus (Fig. 3).—The same technique is followed. It is important to remember that the deeper subcutaneous tissue should be injected and an intradermal or subdermal injection carefully avoided. The amount of Efocaine required for one injection of localized patches (of about 2 to 5 in. [5 to 13 cm.] in diameter) varies from 2 to 5 cc. Local anesthetic infiltrative techniques should not be used over wide areas. Pruritic pain control will be more successfully accomplished by nerve-blocking procedure, carried out by a trained anesthetist.

Results of Treatment with Efocaine

Diagnosis *	Patient,† No.	Amount per Injection, Cc.	Injections, No.	Comment, Relief	
Pruritus ani	18	10	3	Complete ‡	14
				Temporary	2
				No	2
Pruritus ani et vulvae	14	10	2 to 3	Complete	9
				Temporary	3
				No	2
Lichen simplex chronicus	8	2 to 5	1 to 2	Complete	8
Hypertrophic lichen planus	2	5	1	Complete	2
Total	42				

* Duration of dermatoses was from 6 months to 15 years.
† Ages of men were from 31 to 54; ages of women were from 26 to 44.
‡ Complete relief judged at the end of four-month follow-up period.

COMMENT

Forty-two patients with stubborn pruritus were treated with Efocaine. This included 32 patients with pruritus ani and pruritus vulvae. Of these, 23 (71.9%) had complete relief, 5 (15.6%) had temporary relief, and 4 (12.5%) had no relief. The patients listed as treatment failures had no relief after the first injection, and subsequent injections were not attempted.

The relief from pruritus lasted from one to two weeks following each injection. In order to maintain relief, subsequent injections were given. These patients were observed over a four-month follow-up period after the last injection. Eight patients with lichen simplex chronicus and two with hypertrophic lichen planus were treated, with complete relief. Prolonged local anesthesia is not a "specific" for pruritus, nor does it "cure" the pathology. It does, however, interrupt the "itch-scratch; scratch-itch" cycle, providing symptomatic relief long enough to permit healing and to allay the inflammatory reaction of the irritated tissue.

No slough or local toxic tissue-reactions were observed, nor were any abscesses or systemic toxic reactions encountered. Occasionally, an initial transient burning sensation was noted. The use of Efocaine may be carried out on an ambulatory basis in the office and requires no specialized technique. The results obtained in this series indicate that further exploration with this method of therapy, with this drug, is warranted.

SUMMARY

Forty-two patients with pruritic dermatoses were treated by local Efocaine injections; 78.6% gained complete relief, 11.9% temporary relief, and 9.5% no relief.

No untoward local or systemic toxic reactions were observed.

Efocaine has the advantage of not requiring any specialized technique or apparatus for administration, and the administration may be carried out as an office procedure.

GRANULOMA ANNULARE IN IDENTICAL TWINS

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PAWTUCKET, R. I.
AND
WILLIAM B. COHEN, M.D.
PROVIDENCE, R. I.

In the past decade, many papers on dermatoses occurring simultaneously in identical twins have been reported in the dermatological literature. No adequate theory has been advanced for this phenomenon. Sharlit[1] believes that it is merely coincidence. Granuloma annulare is not included in the long list of dermatoses in twins in the 1,381-page treatise of Gedda.[2] Recently, we observed identical twins, both with granuloma annulare (Fig. 1).

Fig. 1.—Paula R. and Pamela R., identical twins.

REPORT OF CASES

Paula R., a 9-year-old white girl, was first seen at the skin outpatient department of the Memorial Hospital, Pawtucket, R. I., in August, 1951, complaining of a lesion located on the left wrist, of one month's duration (Fig. 2). She had always been in good health. There was no incidence of tuberculosis in the family. Examination revealed cutaneous waxy papules, forming an almost complete circle, measuring 2.5 cm. in diameter, on the anterior aspect of the left wrist. The center was clear of lesions but showed some atrophy. A diagnosis of granuloma annulare was made, and x-ray therapy was given.

From the Department of Dermatology and Syphilology, Memorial Hospital, Pawtucket, William B. Cohen, M.D., Chief of Service.

1. Sharlit, H.: Coincidence and Dermatoses, Arch. Dermat. & Syph. **36**:1084 (Nov.) 1937.
2. Gedda, L.: Studio dei Gemelli, Rome, Orizzonte Medico, 1951.

Fig. 2.—Paula R., first twin, showing granuloma annulare on the left anterior wrist.

Fig. 3.—Pamella R., second twin, showing granuloma annulare on the left ankle.

Pamela R., identical twin sister of Paula, seen in April, 1952, at the same clinic, presented a lesion located on the left ankle, of two weeks' duration (Fig. 3). Examination revealed a typical lesion of granuloma annulare. It is to be noted that at the time Pamela was examined, the lesion was still present on Paula. To all outward appearances, the patients were identical twins. No other member of the family was affected.

Laboratory examinations revealed the following findings: Chest roentgenograms, the Kahn test, and urinalyses revealed no abnormalities. Peripheral blood examinations showed normal levels. Tuberculin tests performed in dilutions of 1 to 100,000 and 1 to 10,000 produced no reaction. A biopsy specimen was taken from the skin of each twin, and the report by Dr. H. Fanger, pathologist, Rhode Island Hospital, was as follows:

"Sections of the skin reveal definite degeneration of the collagenous subcutaneous connective tissue. The collagen shows a variability of staining reaction and there is a lymphocytic reaction seen only occasionally about the blood vessels. The fibrous tissue is fragmented and in one of the sections there is a definite granular degeneration of the collagen with the tissue assuming a basophilic staining reaction, associated with which there is a fibroplastic reaction. There are similarly here seen occasional lymphocytes and plasma cells."

A diagnosis of granuloma annulare was made.

COMMENT

The cause of this disease is still obscure. The tuberculous origin formerly believed has never been established. Bugarski's [3] conclusion that granuloma annulare is a photodermatosis caused by the action of the sun through a photocatalyzer which is formed by tubercle bacilli, their toxins, or their secondary products originating in the organism, has never been confirmed by other investigators. Further argument against a tuberculous origin is the absence of tubercle bacilli in sections, and most inoculations in guinea pigs produce negative results even in second passage.

Prunty and Montgomery [4] reviewed 31 cases of granuloma annulare and found no evidence to support a tuberculous origin.

Ellis [5] suggested that granuloma annulare is closely related to, if not identical with, necrobiosis lipoidica diabeticorum. This however, can be invalidated on histological evidence.

Finally, the possibility of cure of granuloma annulare after a biopsy has been done constitutes one more argument against the tuberculous origin of the lesions, and against the disease being closely related to necrobiosis lipoidica diabeticorum. Does the occurrence of granuloma annulare, appearing first in one and then in the other twin, point toward an infectious or contagious causation? There was a definite contact, since the twins were inseparable and shared the same bed. Further, a review of the history reveals an incubation period. However, since transmission of the disease from one person to another has never been reported, this theory must await further investigation.

SUMMARY

A case of granuloma annulare in identical twins is reported. The etiology of this disease is discussed. The possibility of an infectious causation is suggested.

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105 Waterman St. (Dr. Cohen).

3. Bugarski, S.: Etiology and Pathogenesis of Granuloma Annulare, Deutsche med. Wchnschr. **66**:1217-1220 (Nov. 1) 1940.

4. Prunty, F. A., and Montgomery, H.: Granuloma Annulare, Arch. Dermat. & Syph. **46**:394-413 (Sept.) 1942.

5. Ellis, F. A., and Kirby-Smith, H.: Necrobiosis Lipoidica and Granuloma Annulare, Arch. Dermat. & Syph. **45**:40-60 (Jan.) 1942.

NONSURGICAL TREATMENT OF BIRTHMARKS BY TATTOOING

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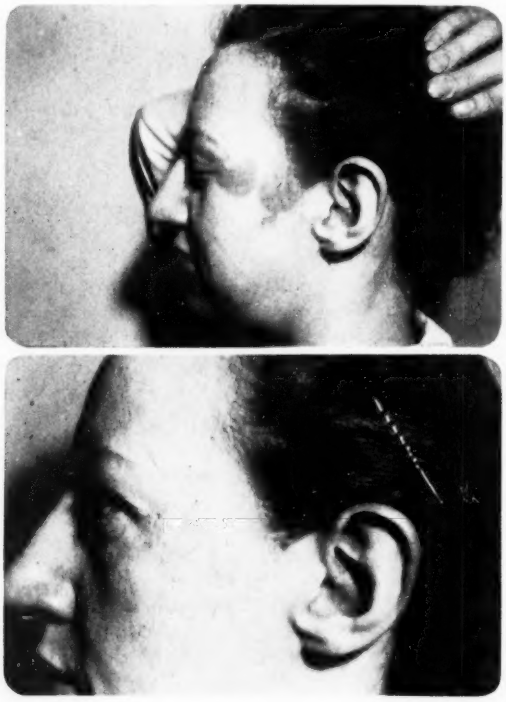
The following report presents a physical method of obliterating a birthmark, or port-wine stain, of the face by intradermal injection of permanent pigments by tattooing. This method was reported by Conway [1] and is executed with the Conway Dermajector, an electrical tattooing machine. I believe that this is a definite improvement in the treatment of certain capillary hemangiomas, the flat port-wine stains due to subdermal and dermal capillary invasion which cause a marked purplish discoloration of the skin through a normal epidermis. Other physical



Above, port-wine stain of the left side of the face before treatment; below, close-up view of nevus almost completely obliterated by intradermal injections of permanent pigments.

methods, such as electrodesiccation, irradiation, and application of solid carbon dioxide are often not successful, and if successful may leave a thin atrophic skin., which condition may be worse than the original lesion. This method of tattooing pigment over the nevus can give a better result than surgical excision of a large hemangioma which has to be replaced by a skin graft from a distant area of the body, which skin does not match the rest of the face and requires cosmetics to cover and camouflage it.

From the Department of Maxillo-Facial Surgery, Michael Reese Hospital.

1. Conway, H.: New York J. Med. **48**:2040-2043 (Sept. 15) 1948. Conway, H., and Docktor, J. P.: Surg., Gynec. & Obst. **84**:866-869 (April) 1947.

In the case shown here, L. B., a 35-year-old white woman, had a birthmark over the left side of her face and ear. This port-wine stain extended from the external canthus of the left eye over the zygomatic and preauricular area of the face and also involved the skin of the anterior and posterior aspects of the ear. The area around the ear presented no problem as the patient's hair covered it, but the facial deformity took many hours of the patient's time to camouflage with cosmetics to avoid embarrassment.

The tattooing of pigments intradermally is done in stages. The equipment, namely, the handle of the instrument, the needles, the brush, and the tray for mixing pigments, is sterilized and the entire technique performed on an aseptic basis. The pigments are mixed in sterile water or 2% lidocaine hydrochloride (xylocaine), a local anesthetic, until the proper color to blend with the patient's facial skin is obtained. The first time, a small trial area only is tattooed. A crust which forms over the area in a few days detaches in 7 to 10 days, and from this one can judge how to treat the rest of the hemangioma, which is covered in areas of about 1 sq. in. (6.45 sq. cm.) at a time. If the pigment is properly injected intradermally it masks out and obliterates the nevus, and the area is now a flesh-colored pigmented area which blends with the surrounding skin and can be covered with face powder as used in everyday face care.

I am at present using the Conway Dermajector on a skin graft of the face and neck which was taken from the thigh to replace a burn contracture of the lower part of the face and the neck. The graft does not match the skin of the face and the neck, so I am tattooing the flesh-colored pigment into the graft. I am also using the Dermajector in a case of vitiligo of the face to tattoo brown pigment into the affected areas to blend them with the rest of the patient's brown skin.

The practice of tattooing is not new, and if a sterile and aseptic technique is used no ill should befall the patient. The case shown here indicates that tattooing has a definite place in the treatment of capillary hemangiomas of exposed parts like the face by obliterating the nevus by intradermal injection of pigments.

CHRONIC DISCOID LUPUS ERYTHEMATOSUS COMPLICATED BY SUPERIMPOSED SQUAMOUS CELL EPITHELIOMA

Report of a Case

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BROOKLYN

M. K., a woman aged 48 years, a graduate nurse by profession, first consulted a dermatologist at the age of 25 because of a lesion on the left cheek. This was diagnosed at that time as chronic discoid lupus erythematosus and "confirmed by biopsy." She received, over a period of 20 years, various forms of conventional therapy for this condition, including injections of gold, bismuth, and liver extract, as well as various types of local therapy, including application of solid carbon dioxide. Her condition fluctuated in its severity, with periods of quiescence lasting several years, interrupted by flare-ups. She stated that these exacerbations were characterized by increased erythema and itching, with some scaling, but that at no time was there any elevation of the lesion above the surface of the skin. The usual appearance until the onset of the present complication was described by her as a flat "scar" covering the left cheek below the eye and extending from the border of the nose out to the malar prominence. During the month of January, 1952, she observed a change in the usual appearance of the lesion. At first the surface became rough. Then followed gradually a progressive elevation of the lesion above the level of the surrounding skin and the lesion became covered by a "warty crust," which the patient was at first able to remove easily. Later this covering became adherent and the entire lesion became "thick and swollen." She was finally forced to seek medical care because of its "appearance." She was first seen by me in September, 1952.

From the Departments of Dermatology and Dermatopathology of the Jewish Hospital,

Fig. 1.—Clinical appearance of lesion.

Fig. 2.—Low-power photomicrograph showing junction area of lupus erythematosus and squamous cell carcinoma.

Fig. 3.—High-power photomicrograph of area of lupus erythematosus. Note atrophy of epidermis, liquefaction of basal layer, and edema of corium, with lymphocytic infiltrate around appendages.

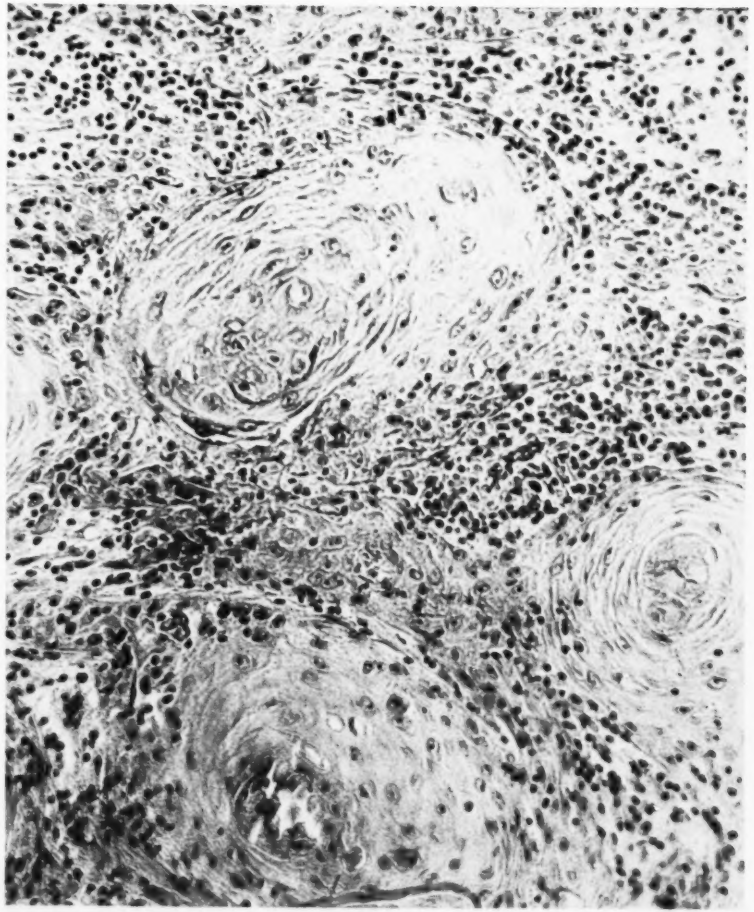

Fig. 4.—High-power photomicrograph from area of neoplasm, showing typical dyskeratosis, pearl formation, and inflammatory infiltrate.

Examination revealed a huge nodular brownish-black growth, lobulated in appearance and rubbery in consistency, covering the entire surface of the left infraorbital fossa. The lesion could be lifted en masse from the underlying panniculus adiposus, and seemed to occupy a scar-like atrophic nest, of which remnants could be seen on the mesial aspect of the lesion extending on to the nose (Fig 1).

A biopsy disclosed changes typical of squamous cell carcinoma.

The lesion was removed by plastic surgery and replaced with a full-thickness skin graft. (It was deemed inadvisable to treat this lesion with radiation for two reasons: (1) presence of an atrophic nidus of lupus erythematosus; (2) possibility of activation of discoid lupus erythematosus into the disseminated variety.)

Histologic examination of the excised specimen showed an area of typical discoid lupus erythematosus, merging abruptly with a fulminating squamous cell carcinoma (Figs. 2, 3, and 4).

COMMENT

Squamous cell epithelioma has been reported as a complication of both lupus vulgaris and lupus erythematosus, but in my experience has been a rare occurrence. This is certainly the most extensive lesion which I have seen, particularly from the standpoint of the rapidity of its development. How much influence the duration of the preexisting lupus erythematosus, as well as all the therapy administered, played in the genesis of the lesion is purely speculative. The case is reported because of its unusual nature.

135 Eastern Parkway.

FAILURE OF SMALLPOX VACCINE IN TREATMENT OF RECURRENT APHTHOUS STOMATITIS

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AND
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Although a viral etiology has been suggested for recurrent aphthous stomatitis,[1] most investigators have not been able to isolate a virus from recurrent aphthous lesions.[2] Some investigators, however, have reported that patients with recurrent aphthous stomatitis were benefited by

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Smallpox vaccine for this study was supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y. through the courtesy of Dr. J. M. Ruegsegger.

1. (*a*) Cahn, L.: Virus Disease of the Mouth, Oral Surg. **3**:1172 (Sept.) 1950. (*b*) Robinson, H. B. G.: Recurrent Lesions of Oral Mucosa, Postgrad. Med. **8**:248 (Sept.) 1950. (*c*) Aphthous Stomatitis, Queries and Minor Notes, J. A. M. A. **141**:362 (Oct. 1) 1949. (*d*) Recurrent Herpetiform Lesions, Queries and Minor Notes, ibid. **141**:299 (Sept. 24) 1949. (*e*) Scott, T. F. M.; Steigman, A. J., and Convey, J. H.: Acute Infectious Gingivostomatitis: Etiology, Epidemiology and Clinical Picture of Common Disorder Caused by Virus of Herpes Simplex, ibid. **117**:999 (Sept. 20) 1941. (*f*) Kilbourne, E. D., and Horsfall, F. L., Jr.: Primary Herpes Simplex Virus Infection of the Adult with a Note on the Relation of Herpes Simplex Virus to Recurrent Aphthous Stomatitis, A. M. A. Arch. Int. Med. **88**:495 (Oct.) 1951.

2. Blank, H.; Burgoon, C. F.; Coriell, L. L., and Scott, T. F. M.: Recurrent Aphthous Ulcers, Correspondence, J. A. M. A. **142**:125 (Jan. 14) 1950. Dodd, K., and Ruchman, I.: Herpes Simplex Virus Not the Etiologic Agent of Recurrent Stomatitis, Pediatrics **5**:883 (May) 1950.

vaccination with smallpox vaccine[3] and particularly by the use of intradermal injections of smallpox vaccine.[4] This study was attempted in an effort to corroborate the latter positive findings.

Each patient presented had a history of recurrent aphthous stomatitis of at least one year's duration (many much longer) and had been observed by us for a prolonged period during the course of placebo and other unsuccessful therapy, some phases of which have already been reported.[5] In no case was any evidence of accompanying skin lesions noted.

METHODS

Five intradermal injections of smallpox vaccine were administered to each of the 12 patients (four men and eight women, aged 27 to 81) with recurrent aphthous stomatitis in the following manner: On the first visit the contents of one-half of one capillary tube of vaccine was mixed with 0.5 cc. of sterile saline and injected intradermally; at the second visit, one week later, the full contents of one vaccine tube was mixed with 0.5 cc. of sterile saline and injected intradermally; at subsequent weekly intervals the contents of two capillary tubes, then three capillary tubes, and finally four capillary tubes were diluted with sterile saline to make up 0.5 cc. of solution and injected intradermally.

RESULTS

Of the 12 patients studied, none has remained permanently free of lesions following therapy. The severity, number, frequency, and duration of the lesions were neither favorably nor adversely affected permanently in any case by smallpox vaccine therapy.

In 3 of the 12 patients there may have been some diminution in the severity of the recurring cycles for two months only. Severe recurrences occurred, however, in two instances. In the other patient, as of the present, recurring attacks continue as frequently as before therapy but with apparently diminished severity.

In three patients the duration of the period of remission following smallpox vaccine therapy was such as to be suggestive at the time of an improved status of the patient. However, the recurrence of lesions within the established time limit (toward the conclusion) for each patient's usual cycle subsequently negated the earlier promising "clinical impressions." Such coincidental occurrences as well as failure to follow cases for sufficient periods of time are probably responsible for reports in the literature which recommend smallpox vaccine therapy for recurrent aphthous stomatitis. It is to be noted that recurrences frequently appeared during active therapy with smallpox vaccine.

SUMMARY

In this series of 12 patients, five intradermal injections of smallpox vaccine, one injection per week for five weeks (totaling 10½ capillary tubes of smallpox vaccine), administered to each patient did not influence the course of recurrent aphthous stomatitis during therapy, nor prevent the recurrence of lesions after treatment. In one patient subsequently recurring attacks have been as frequent as before therapy but apparently not as severe.

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3. Queries and Minor Notes.[1c] Ulcers in Mouth and Throat, Queries and Minor Notes, J. A. M. A. **144**:1419 (Dec. 16) 1950. Oral Aphthae, Queries and Minor Notes, ibid. **142**:954 (March 25) 1950.

4. Robinson.[1b] Recurrent Ulcer of the Mouth, Queries and Minor Notes, J. A. M. A. **137**:1004 (July 10) 1948. Canker Sores, Queries and Minor Notes, ibid. **141**:1339 (Dec. 31) 1949.

5. Zegarelli, E. V.; Silvers, H. F., and Kutscher, A. H.: Systemic Aureomycin in the Treatment of Recurrent Aphthous Stomatitis, New York J. Dent. **18**:137 (March) 1952. Zegarelli, E. V.; Silvers, H. F., and Kutscher, A. H.: Antihistaminic Agents in the Treatment of Recurrent Aphthous Stomatitis, Oral Surg. **6**:302 (Feb.) 1953. Kutscher, A. H.; Budowsky, J., and Chilton, N. W.: Observations on the Clinical Use of Terramycin Troches, Oral Surg. **6**:640 (May) 1953. Kutscher, A. H.; Silvers, H. and Zegarelli, E. V.: Chloramphenicol and Terramycin in the Treatment of Recurrent Aphthous Stomatitis, J. A. D. A. **46**:144 (Feb.) 1953.

NONSURGICAL TREATMENT OF CUTANEOUS BERYLLIUM GRANULOMA

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There appears to be almost unanimous agreement that surgical intervention is the only treatment for cutaneous beryllium granuloma. Nichol and Dominguez [1] advise wide excision of such lesions and warn that the cure of the local lesions can be accomplished only if all beryllium-contaminated tissue is removed. Davis and Grimes [2] and Helwig [3] emphatically agree that surgical excision of beryllium granuloma is mandatory.

Therefore, it seems significant to present a case report in which cutaneous beryllium granulomas healed without surgical intervention.

REPORT OF A CASE

J. P., a man aged *27*, sustained lacerations on two fingers caused by a broken fluorescent bulb known to contain beryllium silicate. The accident occurred on Sept. 5, 1951, and involved the third and fourth fingers of the right hand. The wounds were sutured within one hour after the accident. Two weeks after the wounds had been sutured, the tissues broke down and ulcerated.

Cutaneous beryllium granuloma of five months' duration.

When seen three months later, the patient presented indolent ulcers of the skin over the distal interphalangeal joints of the third and fourth fingers of the right hand. The lesions on the fourth finger extended across the entire dorsal aspect of the phalanx and over onto the mesial surface. The ulcer was 1 in. (2.5 cm.) long and ⅜ in (1 cm.) wide. The ulcer of the third finger was smaller, measuring ½ in. (1.3 cm.) long and ¼ in. (0.6 cm.) wide, and covered the lateral surface of the finger. Both lesions were very tender to touch and were surrounded by an erythematous, infiltrated zone. The granulation tissue at the base of the ulcer was dull red and did not bleed easily.

A roentgenogram of the fingers of the right hand revealed a marked soft tissue swelling on the dorsal and radial aspect of the distal interphalangeal joint of the right ring finger. There was no evidence of any destructive lesions, but there was osteoporosis of the middle phalanges and distal phalanges of the right ring finger as compared with the other fingers.

1. Nichol, A. D., and Dominguez, R.: Cutaneous Granuloma from Accidental Contamination with Beryllium Phosphors, J. A. M. A. **140**:855-860 (July 9) 1949.

2. Davis, C., and Grimes, O. F.: Skin Granuloma Following Laceration by a Fluorescent Lamp, California Med. **74**:203-205 (Jan.) 1951.

3. Helwig, E. B.: Chemical (Beryllium) Granulomas of Skin, Mil. Surgeon **109**:540-558 (Oct.) 1951.

The histologic examination revealed that part of the tissue had an acanthotic epidermis, which formed the margin of a granulomatous ulceration. The entire cutis consisted of thickened small blood vessels with perivascular infiltration composed of small round cells, histiocytes, and some plasma cells. There were also masses of lighter-staining epithelioid cells and epithelioid giant cells. The microscopic diagnosis was, "consistent with beryllium granuloma."

Four months after the injury was sustained, in January, 1952, the patient was presented before the Bronx Dermatological Society with the lesions essentially unchanged. There was a general agreement that the lesions were beryllium granulomas, and that the ulcers should be widely excised and plastic repair should be performed. The patient, however, refused surgical intervention. Boric acid ointment was applied to both lesions, and the distal interphalangeal joints of the third and fourth right fingers were immobilized with wooden splints. One month after this treatment was instituted, the smaller lesions on the middle finger had healed. However, the larger ulcer on the fourth finger had remained unchanged (Fig.). If anything, the finger was more tender and the zone of erythema was more pronounced.

An ointment consisting of 5% cortisone in an oxycholesterol-petrolatum ointment (aquaphor) was then prescribed. The patient was instructed to massage the ointment into the lesion twice daily and to keep the lesion covered with the ointment in the intervals between massage. The finger was no longer splinted. Ten days after the first application of the cortisone ointment, the lesion became less tender, and the zone of erythema less marked, and there seemed to be some evidence of healing of the ulcer. The improvement continued steadily, and two months later the lesion had healed completely. A roentgenogram at this time revealed that the previously reported osteoporosis had cleared. When the patient was re-presented at the Bronx Dermatological Society on April 17, 1952, the lesions of both fingers were healed.

Reexamination in November, 1952 (six months later) showed that the fingers remained healed.

COMMENT

Persistent granulomatous inflammation of the skin with ulceration may follow lacerations by fluorescent light bulbs coated with beryllium powders (phosphors). Dutra [4] demonstrated typical granulomas in the skin and subcutaneous tissues of pigs following the implantation of fluorescent powder, thus showing experimentally that compounds of beryllium are related to such lesions. Further proof of the relationship of beryllium phosphors to granulomatous skin lesions is found in spectrographic analysis of granulomatous tissue for beryllium.[1] Helwig [3] reports that in man the tissue response to direct injury by beryllium-containing fluorescent lamps is a biphasic reaction characterized by granulomas composed of epithelioid cells, and necrobiotic changes characterized by acidophilic anuclear cells. Although either of these two changes may occur singly in a variety of granulomas, the combination of the two is strong persumptive evidence of chemical (beryllium) granuloma.

The use of cortisone ointment topically has not been reported for cutaneous beryllium granuloma. In general, the topical application of cortisone ointment in dermatology for other conditions has been attended by failure.[5]

There have been several reports on the use of corticotropin or cortisone in chronic beryllium poisoning and pulmonary granulomatosis. Van Ordstrand and his associates [6] treated six such conditions with corticotropin with a moderate degree of temporary improvement. Kennedy and others [7] obtained temporary subjective and objective improvement in two patients with chronic

4. Dutra, F. R.: Experimental Beryllium Granulomas of Skin, A. M. A. Arch. Indust. Hyg. **3**:81-89 (Jan.) 1951.

5. Sternberg, T. H.; Newcomer, V. D., and Linden, I. H.: Treatment of Atopic Dermatitis with Cortisone, J. A. M. A. **148**:904-907 (March 15) 1952. Goldman, L.; Thompson, R. G., and Trice, E. R.: Cortisone Acetate in Skin Disease: Local Effect in the Skin from Topical Application and Local Injection, A. M. A. Arch. Dermat. & Syph. **65**:177-186 (Feb.) 1952.

6. van Ordstrand, H. S.; de Nardi, J. M., and Schneider, R. W.: Chronic Beryllium Poisoning (Chronic Pulmonary Granulomatosis): Preliminary Reports on 4 Cases Treated with ACTH, Cleveland Clin. Quart. **18**:48-54 (Jan.) 1951.

7. Kennedy, B. J., and others: Effect of Adrenocorticotropic Hormone (ACTH) on Beryllium Granulomatosis and Silicosis, Am. J. Med. **10**:134-155 (Feb.) 1951.

beryllium granulomatosis. Hardy [8] reports temporary reversal of x-ray densities in the lung in a few cases following the use of corticotropin or cortisone in pulmonary beryllium granulomatosis, and speculates as to whether such improvement is due to dissipation of the cellular infiltration which prevents oxygen from reaching the tissues in this disease. Dobson [9] also speculates that corticotropin and cortisone may destroy or diminish the cellular reaction around granulomas, thus making it possible to remove the substances that are producing the granulomas.

Although there was no spectrographic examination of the involved tissue for beryllium made in this case, the evidence is strong that the ulcerations were due to beryllium. The patient's laceration was caused by a fluorescent tube known to contain beryllium phosphors, and the histologic examination was consistent with beryllium granuloma. The clinical appearance and course were typical for cutaneous beryllium granuloma.

The smaller lesion healed with simple ointments and immobilization for one month. When the larger ulcer persisted, cortisone ointment was applied topically because of the reports of temporary improvement of pulmonary beryllium granulomatosis with corticotropin or cortisone administered systemically.

SUMMARY

A small cutaneous beryllium granuloma of the finger which had persisted for five months healed with the application of boric acid ointment and immobilization for one month.

A larger cutaneous beryllium granuloma on an adjacent finger, which did not improve with the simple ointment and immobilization that had healed the smaller ulcer, healed after two months of treatment with 5% cortisone in oxycholesterol-petrolatum ointment applied topically.

8. Hardy, H. L.: The Character and Distribution of Disease in American Industries Using Beryllium Compounds, Proc. Roy. Soc. Med. **44**:257-262 (March) 1951.

9. Dobson, R. L.: General Discussion on the Treatment of Chronic Beryllium Poisoning with ACTH and Cortisone, A. M. A. Arch. Indust. Hyg. **3**:629-630 (June) 1951.

SYCOSIS BARBAE DUE TO TRICHOPHYTON RUBRUM (PURPUREUM)

Report of a Case

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In modern cities tinea barbae is today an uncommon skin disorder and therefore is not frequently encountered even in large metropolitan clinics. Lewis and Hopper [1a] state that it is rarely seen in the United States and is uncommon in New York City. By far most cases of folliculitis of the bearded area are bacterial in origin, and according to the literature infections of the upper lip are rarely due to fungi.[1] The following case appears worthy of being reported because it simulated a common form of folliculitis of the upper lip, but later was proved to be caused by fungi.

REPORT OF CASE

J. Mc., aged 34, a salesman, was seen on May 5, 1952, complaining of an infection of the upper lip. In July, 1951, he had first noticed a few isolated "pus pimples" on his chin and lower lip. He consulted his family physician when in September, 1951, a great deal of swelling suddenly developed about the affected areas on his face. This subsided after several weeks of

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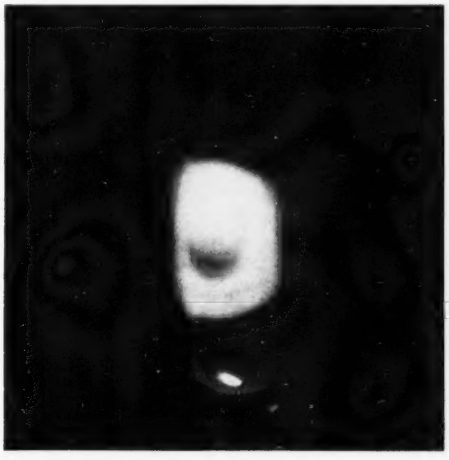
1. (*a*) Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Ed. 3, Chicago, The Year Book Publishers, Inc., 1948. (*b*) Greenbaum, S. S.: Dermatology, Diagnosis and Treatment, Philadelphia, F. A. Davis Company, 1949. (*c*) McCarthy, L.: Diagnosis and Treatment of Diseases of the Hair, St. Louis, C. V. Mosby Company, 1940. (*d*) Conant, N. F., and others: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1944.

treatment, and the eruption reverted to its former state, namely, that of a few scattered "pimples" over the bearded areas. In March, 1952, he noted for the first time involvement of the upper lip. Gradually, as the upper lip became more prominently involved, the lesions on the rest of the face seemed to clear. The patient was aware that the hairs at the affected sites could be pulled out easily.

The past history revealed a recurrent "athlete's foot" infection, which was readily controlled by benzoic and salicylic acid ointment (Whitfield's ointment), and a "jock itch," which had not troubled him for many months. Penicillin troches taken a few months previously for a sore throat had produced a severe swelling of his tongue.

On examination the upper lip showed an erythematous papular and pustular eruption with some crusting, and there were a very few erythematous papular lesions on the cheeks. The lesions were superficial, and each one was pierced by a hair. There was no evidence of any circinate scaling or nodular lesions at that time. The groins showed some erythematous, scaling, circinate patches; and the interdigital webs of the toes, particularly between the fourth and fifth toes, were scaly and slightly macerated. Over the buttocks and extending to the lumbosacral



Trichophyton rubrum culture.

area of the back and on the upper posterior thighs, there was a very large confluent and well-defined brownish pigmented area with a purplish red, somewhat scaly, border. The nails appeared normal.

The diagnosis of tinea barbae was considered, only to be put aside in favor of sycosis vulgaris in view of the clinical appearance of the eruption. Aureomycin ointment was prescribed in addition to the usual instructions for a folliculitis of the beard. After about four days the patient returned much worse than when he was seen originally. His upper lip was swollen, and many of the papular lesions had become pustular and more deeply infiltrated. On the left side of the lower lip an erythematous, scaly, arciform lesion was noted. Scrapings and hairs were taken for fungus examination, including culture on Sabouraud's medium. The patient was instructed to use warm boric acid compresses and iodochlorhydroxyquinoline (Vioform) ointment, and to discontinue the use of aureomycin ointment. In addition he was given a resorcinol lotion for his groins and Whitfield's ointment for his toes.

Mycologic examination of the scrapings from the lower lip area, on direct examination in 10% KOH, showed mycelial filaments. Similar examination of an infected hair revealed an ectothrix fungus with large spores. The culture early showed a white fluffy point about the root of the hair. Later the growth became hemispheric, pure white, and velvety (Figure). The substrate pigment was centrally located beneath the growth and was of a dark purple color. Thus the fungus was identified as Trichophyton rubrum (purpureum). Intracutaneous injection

of 0.1 cc. of 1:30 trichophytin produced an immediate wheal response. The site after 24, 48, and 72 hours was negative.[2]

There was only slight improvement when the patient was seen again on May 16, 1952. Solution of sulfurated lime (1:33) compresses were prescribed in place of boric acid compresses, and a 3% resorcinol tincture was advised instead of the iodochlorhydroxyquinoline ointment. When he was seen four days later, there was decided improvement. The lip was no longer swollen, the pustules had disappeared, the infiltrations were receding, and the arciform lesion on the lower lip area was practically gone. Further management consisted of manual epilation of the hairs suspected of being infected, and continued use of compresses of solution of sulfurated lime and resorcinol and salicylic acid tinctures. There was progressive improvement, and finally apparent cure of the disease.

COMMENT

With the advent of the safety razor and the improvements in hygiene in general, the incidence of tinea of the beard has taken a sharp decline. In any event, this condition today is among the less common dermatoses,[3] and when the process simulates sycosis vulgaris it is difficult to detect.[4]

It is a common error to assume that pustular eruptions are almost always bacterial in nature.[5] As it turned out in the patient reported on here, this assumption, however, proved somewhat helpful. The antibiotic thus prescribed, perhaps by suppressing the resident bacterial flora in the skin, produced activation of the fungous infection, and this in turn led to the correct diagnosis. The presence of sycosis largely on the upper lip was misleading at the time of the patient's original visit, for most authors state that involvement of the upper lip is helpful in differentiating tinea barbae from sycosis vulgaris. McCarthy, however, states that this has not been his experience.[1c]

Treatment of fungous infections of the beard would be expected to follow the lines laid down for tinea capitis. However, in the case reported here, ointments were poorly tolerated. Lewis and Hopper[1a] mention that strong topical applications are to be avoided, particularly in the form of ointments. The scalp is more resistant to irritation than the face and, of course, can withstand much stronger topical therapy. X-ray epilation of the beard is not advocated because of the difficulty in obtaining a defluvium without producing a radiodermatitis. MacKee and Cipollaro[6] advise against it whenever possible. Manual epilation, however, is useful and safe, and was successfully employed in this case, in conjunction with topical therapy. Very effective as local treatment were compresses with solution of sulfurated lime (1:33) and the application of resorcinol and salicylic acid tincture. Anthralin in 0.25% strength has been successfully used by some, but its staining qualities and the care necessary to avoid any irritation of the eyes, impair its practicability. Mercury in the forms of the white precipitate or as red mercuric sulfide (cinnabar) is another antifungal agent used in the sycosis type of infections.

SUMMARY

In modern cities tinea barbae is today an uncommon skin disorder. In some cases, because of its clinical appearance, it is easily confused with sycosis vulgaris. A case of this type in which the process was limited mainly to the upper lip has been presented.

This localization is frequently considered a clinical finding in favor of a bacterial rather than of a mycotic sycosis. When antibacterial treatment with aureomycin ointment was instituted, the eruption became worse, and this event altered the original clinical diagnosis of sycosis vulgaris to that of tinea barbae. Proper antifungal therapy controlled and apparently "cured" the process.

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2. Lewis, G. M.; Sulzberger, M. B., and Wise, F.: Trichophytin and Allergy to Trichophytin: Observations on Variability of Cutaneous Responses to Trichophytin, Arch. Dermat. & Syph. **36**:548, 1937.

3. Muskatblit, E.: Personal communication to the author.

4. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Ed. 7, Philadelphia, Lea & Febiger, 1948.

5. Sulzberger, M. B., and Baer, R. L., Editors: The 1951 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1952.

6. MacKee, G. M., and Cipollaro, A. C.: X-Rays and Radium in the Treatment of Diseases of the Skin, Ed. 4, Philadelphia, Lea & Febiger, 1946.

Society Transactions

CHICAGO DERMATOLOGICAL SOCIETY

James R. Webster, M.D., *President*
Irene Neuhauser, M.D., *Secretary*
Nov. 19, 1952

Sarcoidosis (by Biopsy). Presented by Dr. Theodore Cornbleet, Dr. Henry Schorr, and (by invitation) Dr. J. F. Sickley.

The patient is a 28-year-old Negro woman. In June she noticed many small papular lesions on her forearms. At the onset of the eruption there was slight pruritus, but since this time the lesions have been asymptomatic. Since the patient first noticed the papules they have not increased in size, and very few new lesions have appeared.

The patient has felt well, and her appetite has been good. She has lost about 20 lb. (9 kg.) of weight in the past six months, but she states this occurred after an operation for "fibroid tumors."

Physical examination revealed the following findings: At present the patient has multiple small flesh-colored papular lesions on both forearms and a few scattered lesions on the upper arms. There are no similar lesions on the lower extremities or body. There are multiple pigmented papular lesions present on the face, but these have been present since childhood.

There is no remarkable adenopathy.

Laboratory tests gave the following results: Urinalysis gave negative results for albumin and sugar. Results of blood studies were as follows: hemoglobulin, 79%; red blood cells, 5,000,000; white blood cells, 5,300; with differential count of 48% polymorphonuclears, 40% lymphocytes, 9% monocytes, 1% eosinophiles and 2% basophiles.

Serologic reactions for syphilis were negative. Total proteins were 6.7 gm. per 100 cc.; albumin 4.3 gm., globulin 2.4 gm.

X-ray of the chest showed no radiographic evidence to suggest pulmonary sarcoidosis. X-rays of both hands reveal no cystic lesions or the presence of fine reticulation.

Biopsy revealed sarcoidosis.

Sarcoidosis? Presented by Dr. Theodore Cornbleet, Dr. David Cohen, and (by invitation) Dr. Stefan Bielinski.

The patient is a 64-year-old Negro who states that in 1930 a raised red patch about the size of a dime developed on his right cheek. The patch enlarged very slowly. About a year later a similar lesion developed on the left cheek. Swelling of the soft tissue just below both lower eyelids also developed. All these lesions persisted and enlarged very slowly. In 1934 the swelling below the left eye was incised, and a "fibroid tumor" was removed. Shortly afterward he noticed similar patches developing on the right arm and the back. The eruption starts as a small raised "bumpy" lesion which gradually enlarges by peripheral extension. The center of the lesion remains elevated but becomes smoother. The advancing border consists of raised nodules. Evolution is extremely slow, requiring many years to reach the present size.

In 1940 an incision and curettage of the pedunculated lesion below the left eye were done a second time. In 1941 a patch developed on the left arm. The most recent lesion, which he noticed in 1950, is a dime-sized patch over the right patella.

Occasionally the masses below the eyes and the periorbital tissues have become swollen, and this causes a "stinging pain." Otherwise the lesions have been nonsymptomatic.

The patient states that he was born in Louisiana, 30 miles (48 km.) north of Baton Rouge, in 1888. He lived in and migrated about Louisiana until 1922, when he moved to Mississippi. He lived there until he moved to Chicago, in 1940. He has never been outside of the U. S. A. and has no knowledge of a similar eruption in the family or in the communities where he lived.

In 1930 he was treated for syphilis with "hip and arm shots" for about four months. He had treatment again in 1945, but stopped treatment after three weeks.

One year ago he weighed 135 lb (61 kg.). His present weight is 121 lb. (55 kg.).

The patient presents a symmetrical eruption involving the lower two-thirds of the forehead, the eyelids, the cheeks, and the nose. The involved areas are raised and indurated. The borders are sharply demarcated and consist of coalesced nodules. There are also nodules scattered over the central portions of the lesions. On the upper eyelids there are multiple small papules. On the malar prominences below both eyes are soft, "bag-like" masses, the left being pedunculated and causing a mild ectropion of the left lower eyelid. There is a sparsity of hair of both eyebrows. There is a similar infiltrated circular patch about the size of a half dollar placed centrally over the protruding portion of the chin. The eruption of the face suggests a lionine facies.

There are similar infiltrated plaques on the extensor surfaces of both arms, the right lumbar area, the right ear, and over the right patella.

There are moderately enlarged lymph nodes in both femoral regions and in the right epitrochlear area and smaller glands palpable in each axilla and in the left epitrochlear area.

The ulnar nerves are palpable in the ulnar grooves, but do not seem enlarged. Deep tendon reflexes are all present and normal. No pathological reflexes were elicited. Heat, cold, pain, and touch sensations were normal in both the erupted areas and the normal skin throughout the entire body. Coordination tests showed normal findings. The Romberg sign gave a negative result.

There is a slight scar on the right side of the coronal sulcus, the site of an old healed penile lesion.

Urinalysis gave negative results. The hemoglobin content was 82%. The white blood cell count was 4,800.

Total proteins were 7.6 gm.; albumin 4.1 gm., globulin 3.5 gm. Results of the Kahn and Wassermann tests were positive.

The reaction to the tuberculin test was negative in dilutions of 1:1,000 and 1:100. The lepromin test gave a negative result.

X-ray of the chest revealed a calicified pleural plaque on the left.

X-ray of the hands revealed a small cyst in the middle phalanx of the left ring finger.

Eye consultation showed no evidence of ocular sarcoidosis. The fundi revealed severe retinal arteriosclerosis.

Biopsy of the skin revealed sarcoidosis.

Nasal smears for acid-fast bacilli gave negative results.

DISCUSSION ON CASES OF SARCOIDOSIS

DR. ADOLPH ROSTENBERG JR.: The chief problem with sarcoidosis is how to diagnose it. Before saying a word about that, I think that we as dermatologists are too often guilty of what I am convinced is an error: the failure to differentiate between the concept of sarcoid and sarcoidosis. The term "sarcoid" should be used to denote a pathologic picture which can be initiated by a number of heterogenous stimuli, one of which is the etiologic agent of the disease "sarcoidosis." The pathologist is not able to make the diagnosis of "sarcoidosis." All he can tell you is that the findings are compatible with that diagnosis.

As to the first case, I cannot see any reason why it should be labeled sarcoidosis. There are no lung changes and no blood changes. No information is given as to the tuberculin reaction. All one can say is that the patient had some sarcoid changes, but what caused the sarcoid changes is something that has yet to be determined.

As to the second case, there is much more evidence for sarcoidosis. There were bone changes in some of the fingers. There were some lung findings, though not those particularly associated with sarcoidosis. The patient was anergic to old tuberculin.

Epidemiologically, there is a disproportion in the distribution of cases of sarcoidosis in this country. There are many more cases from the southeast section of the country. Also, there are more cases in rural than in urban communities.

A word as to the immunology: I pointed out in an article in the A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY that there was no theoretical basis for the theory of positive anergy. Since then there has been some experimental evidence against that view. Our work at Illinois has shown that the person with sarcoid has no different ability for disposing of tubercle bacilli (BCG vaccine) than the person without sarcoid (Rostenberg, A., Jr., and others: Experimental Studies on Sarcoidosis, A. M. A. ARCH. DERMAT. & SYPH. **67**:306, 1953). In the June, 1952, *Yale Journal of Biology* there was an interesting article on the reaction to tuberculin and other antigens in sarcoidosis. When the patients with sarcoidosis failed to react to tuberculin they by and large did not react to the other antigens either.

DR. THEODORE CORNBLEET: I cannot see the logic of limiting sarcoid to involvement of some one tissue or organ and reserving the term sarcoidosis for a wider distribution. This would provide the embarrassment of placing limits of where one begins and the other ends. It seems to me more sensible to think of this as one process—and no doubt it is—and one name, differing only in extent and rate of progression. Latterly many of us are treated to the uneasiness of having our experts in histopathology refusing to commit themselves even when a sarcoid or sarcoid-like picture is indicated, because syphilis, leprosy, and what not may thus be masquerading. We can only hope something will happen to bring order out of this seemingly new chaos and restore for some of us our former security about what constitutes sarcoidosis.

Blastomycosis. Presented by DR. HERBERT RATTNER, DR. HAROLD RODIN, and (by invitation) DR. STEFAN BIELINSKI.

A 58-year-old white man states that a blister developed at the tip of the right third toe in April, 1952. The blister broke, and a raised red growth developed. The toe became tender and swollen. A physician treated it with foot soaks and topical medication, without improvement, and another physician then performed a biopsy. The lesion was then "burned off," but recurred in a few weeks. Shortly afterward similar lesions developed on the fourth and fifth toes of the same foot.

In July the patient cut his chin while shaving. The laceration was superficial but would not heal, and it has persisted until the present time. In the past month it has become covered with a crust.

On Aug. 25 he was admitted to a surgical ward and a biopsy of the toe lesion showed "a low grade infiltrating squamous cell carcinoma with marked inflammatory changes," and on Sept. 12 a transmetatarsal amputation of the foot sparing the great toe was done. Serial examination of the amputated specimen then showed "possible histoplasmosis."

The patient was then seen on dermatological consultation.

He has lived in Chicago for 30 years and is a painter and decorator.

Physical examination revealed the following findings: The patient presents a crusted lesion about 7 mm. in diameter on the mentum. Removal of the crust reveals an irregular ulceration.

There is a diagonal transmetatarsal amputation of all the toes of the right foot except the great toe. The operative site is completely healed. There is no adenopathy.

A chest x-ray showed no pulmonary pathology.

Biopsy of a specimen from the chin revealed blastomycosis.

DISCUSSION

DR. M. R. CARO: The unhappy course in this case reminded me of a patient who was seen at the University of Illinois several years ago. The patient was referred to us for the treatment of a lesion on the nose, which had been diagnosed histopathologically elsewhere as epidermoid carcinoma. We made a smear from a pustule at the border and found Blastomyces, and the patient recovered after treatment with potassium iodide. In this case one of the more serious pitfalls of dermatopathology is shown, that everything that suggests carcinoma is not necessarily carcinoma. It is a very good plan to examine several sections, and to examine them very carefully, with a high-power lens to make certain it is not blastomycosis. Even one case like this is one too many.

DR. A. W. STILLIANS: This case reminded me of a case which Dr. Pusey encountered in the early days. One of the surgeons made a diagnosis of sarcoma of the leg and was about to amputate, when the patient got into Dr. Pusey's hands. He made a diagnosis of blastomycosis and saved the man's leg.

DR. C. W. FINNERUD: When we used to have many cases of blastomycosis around here, 20 years ago, and we always had a patient or two on hand for demonstration to the students, we did not rely upon demonstrating the organisms in the histologic section but upon careful search in the miliary abscesses. I still think that that is the surest way of demonstrating the Blastomyces. By persistent search the organisms can almost always be demonstrated in hydrate fresh preparations.

DR. J. B. HAEBERLIN JR.: This patient was seen in our office before the amputation, and the organisms were demonstrated in potassium hydroxide preparations. A biopsy was made, and a diagnosis of blastomycosis was made on the foot lesions before amputation. The patient did not respond to potassium iodide. We were waiting to start treatment with Stilbamidine (4,4'-stilbenedicarboxyamidine), when he was lost from observation.

DR. H. H RODIN, South Bend, Ind: I believe that the discussers have adequately covered the points we had in mind, first, the haste of the surgeons to operate, and secondly, the inadequacy of general pathologists in recognizing pseudoepitheliomatous hyperplasia. Actually, the section on which they made a diagnosis of epithelioma showed Blastomyces in the giant cells. The third point is that we should like to present the patient before and after Stilbamidine (4,4'-stilbenedicarboxyamidine) therapy.

Secondary Syphilis. Presented by DR. THEODORE CORNBLEET, DR. HENRY SCHORR, and (by invitation) DR. J. F. SICKLEY.

DISCUSSION

DR. LEON GOLDMAN, Cincinnati (by invitation): We have been interested in the technique for using fountain-pen ink in demonstrating spirochetes. This will be reported by Dr. Edward Emura of my department. Parker Blue-Black No. 51 ink is used, and it is mixed with the serum from the lesion and fixed by drying. We have been interested in finding the factor in the blue-black ink which actually produces the staining. It is important to emphasize that this is actual staining, not contrast-staining, as produced by India ink. This ink stain is simple, and one can use it on a patient who wanders into one's office with the mistaken idea that he is going to a general practitioner.

Chronic Discoid Lupus Erythematosus Treated with Quinacrine Hydrochloride (Atabrine Dihydrochloride). Presented by DR. SAMUEL J. ZAKON.

A 36-year-old white woman has had an eruption of the face and scalp for the past six years. The eruption became more acute last summer, when the patient exposed herself to the sun.

Physical examination on July 28, 1952, disclosed the presence of sharply defined erythematous scaly round-to-oval patches on the scalp, retroauricular areas, nose, cheeks, and forehead. There was pronounced follicular plugging. The lesions presented the classic features of the discoid type of lupus erythematosus.

The patient was hospitalized on Aug. 3. Routine physical examination did not disclose any abnormal findings.

Biopsy specimen of the skin showed a picture which was compatible with chronic lupus erythematosus. L. E. cells were not found in the sternal bone marrow.

On Sept. 18 the patient was given quinacrine hydrochloride (Atabrine dihydrochloride) therapy, 300 mg. per day for seven days and then 200 mg. every day. There is a deep-yellow discoloration of her skin and a marked fluorescence of the nails. The lesions have improved markedly.

DISCUSSION

DR. HAROLD SHELLOW: I have under observaiton a man with typical chronic discoid lupus erythematosus who presented patches below the ears and extending around to the neck in which huge comedone-like dry follicular plugs were present in great numbers, as they were on the

lobes of his ears. He had an accompanying severe solid edema-like involvement of the ears, so much so that the ears were almost cartilaginous in stiffness. They hardly flexed at all and were painful to simple manipulation. I gave him bismuth intramuscularly, and the lesions underwent some involution. Subsequently, I gave him 0.1 gm. of quinacrine hydrochloride three times daily, and there was a striking and dramatic response, so much so that the ears subsided to about one-third their original size and the follicular plugs greatly diminished. His ears began to become soft and flexible, and it was the first time in six or seven years that he was without pain and could put on his hat without discomfort.

DR. HERBERT RATTNER: I gather from reading recent society transactions that quinacrine is being used with increased frequency for the treatment of discoid lupus erythematosus. I should judge that already some 150 patients have been treated in this country. Sulzberger and his associates made the statement that quinacrine is the best or one of the best treatments we have today. There have already been reported two or three cases of quinacrine dermatitis, but one should recall that all drugs beneficial to lupus erythematosus may produce toxic effects. The experience in Europe, according to Dr. Belisario, is that about one-third of the patients responded exceptionally well to treatment, one-third fairly well, and one-third not at all. When gold therapy was first introduced it also produced excellent results; then reactions were reported, the dose was lowered, and enthusiasm for the drug waned. It is for that reason apparently that some of the more experienced observers show something less than all-out enthusiasm for quinacrine though nobody apparently condemns its use.

DR. GEORGE C. WELLS (by invitation): We have had good results so far in 9 out of 12 cases of chronic discoid lupus erythematosus in which there was treatment with quinacrine. One must certainly be on the look-out for toxic effects, but I do not think that these will prove more serious than with gold therapy; experience with quinacrine as an antimalarial drug supports this view.

DR. STEPHEN ROTHMAN: I do not believe that we can talk of many effective kinds of treatment of chronic discoid lupus erythematodes. Only gold has been really curative in about 80% of the cases. Quinacrine is the second drug which can be regarded as truly effective. I understand that serious complications of prophylactic quinacrine treatment of malaria was seen only in the Pacific theater of war, where high doses were given, and not in the Mediterranean.

DR. M. R. CARO: In all the discussions the fact seems to have been lost that the first two cases of quinacrine-type lichen planus were presented before this Society by Dr. Senear and by me in a man and wife in whom hypertrophic lichen planus developed within 30 days after they had taken quinacrine. Dr. Mitchell obtained the history that they had taken quinacrine, and he helped to establish the etiology of the cases. At that time the Army was against having quinacrine blamed, and the report was withheld for a long time. One need take quinacrine for a very long time for complications to develop, and one need not be in the South Pacific. Our patients had never been away from the vicinity of Chicago.

DR. M. J. BRUNNER: With regard to quinacrine dermatitis in the Mediterranean theater of war, Nelson has reported a number of cases from a general hospital in Italy. It is true that there were fewer cases of quinacrine dermatitis in the Mediterranean theater than in the Pacific. That stems from the fact that the soldiers were considerably more lax in taking quinacrine, since malaria was much less common there than in the South Pacific.

DR. STEPHEN ROTHMAN: Dr. Brunner's explanation is enlightening and very satisfactory.

DR. THEODORE CORNBLEET: The apparent increased resistance of lupus erythematosus to older remedies such as gold needs statistical correction. From the total pool one snatches cases for retrial with a drug that previously failed. No drug, no matter how effective, is perfect. Thus, there remain a residue of cases in which there is resistance to that drug. In the other cases cure is obtained, and the patients are removed from consideration. New effective drugs seem more effective because they have all-available subjects, both sensitive and resistant. This idea is much more easily expressed mathematically.

DR. J. M. MCCUSKEY, Peoria, Ill.: Another interesting feature is that hair had grown in the patches of lupus erythematosus in the scalp. It is a common impression that such alopecia

is permanent, but this is not always true. The history does not state how long the scalp has been involved. It would be interesting to know whether after six years hair has grown in these patches.

I hesitate to prolong the discussion except to state that we feel that we now have a new drug that is probably going to find a place in the treatment of lupus erythematosus. We should remember that this drug will be taken by the patient himself. The prescriptions should not be refilled without the physician's knowledge. The patients should be checked periodically, because we will have a recurrence of these lichenified dermatoses due to the use of quinacrine. Just a few months ago I saw a patient with a lichenified dermatitis and the typical yellow color due to the use of quinacrine. He was a traveling salesman and had taken quinacrine for lupus erythematosus of the face. The result was excellent, and he was so pleased to be free of his lupus erythematosus that he did not seem to mind the yellow color or the large areas of lichenoid dermatitis.

DR. S. J. ZAKON: In spite of the deep-yellow discoloration of the skin, the patient is well pleased with the clinical improvement of her lesions.

One must keep in mind that quinacrine may cause a number of complications; hence, the patient must be observed at frequent intervals. So far this patient feels well, works every day, and there are no changes in her blood cell count. The areas of alopecia of the scalp were of recent origin; hence, the regrowth of hair.

DR. A. M. BUCHHOLZ: As far as is known by H. M. Bloom, who has done work on photosensitization substances, there is no such effect from quinacrine.

DR. G. C. WELLS: Dr. Page, in his original paper, described how he compared the erythema threshold to ultraviolet light in persons before and after giving quinacrine hydrochloride (Atabrine dihydrochloride). The tolerance to ultraviolet light was increased about threefold with quinacrine.

Pretibial Myxedema with Hypertrichosis in Exophthalmic Goiter. Presented (by invitation) by DR. JACK RODRIQUEZ and (by invitation) DR. GEORGE C. WELLS.

DISCUSSION

DR. JACK RODRIQUEZ (by invitation): In the literature I found only one other case in which hypertrichosis occurred. In this report Richter, in the Society transactions of the Berlin Dermatological Society, June 14, 1932, described one case of circumscribed myxedema with hair growth occurring within the lesion. This is the only case I was able to find outside of our own in which hypertrichosis occurred all over the legs. Hair growth was also excessive in the pubic region, where the patient said it had grown so long that she had to cut it off. Hair growth on her face is quite prominent.

According to the reports the occurrence of pretibial myxedema occurs in treated exophthalmic goiter In eight cases reported by Dr. Paul O'Leary, seven occurred approximately six months after treatment. In one case the circumscribed myxedema itself occurred approximately six months before any signs of hypothyroidism had developed. It was the only case I know of in which the myxedema itself occurred before signs of hypothyroidism were present. We do not know the explanation for the hypertrichosis.

Facial Granuloma with Eosinophiles (Eosinophilic Granuloma). Presented by DR. MICHAEL H. EBERT.

DISCUSSION

DR. H. M. BULEY, Champaign, Ill.: Dr. Ebert's case is an unusually fine example of facial granuloma with eosinophilia. The picture presented by this patient may be called characteristic to a great extent, although I realize that it is always somewhat dangerous to use the word "characteristic" in describing something the nature of which is actually unknown. The fairly symmetrical distribution of the eruption on the face closely resembled discoid lupus erythematosus, and on superficial examination this patient's dermatosis might have been mistaken for such. The absence of scales, follicular spikes, and atrophy, however, readily excluded that diagnosis.

The histological picture was also typical. Only one finding was unusual, namely, the presence of hemosiderin deposits within the granulomatous area. Since the specimen, however, was taken from a small lesion near the frontal hairline, it is conceivable that it was traumatized by combing or scratching, resulting in small hemorrhages into the tissue.

The disease is completely benign, and from the few cases encountered in recent years we have learned that it usually follows an extremely chronic course, often over a period of 10, 20, or more years.

As far as the treatment of this condition is concerned, x-ray therapy has been beneficial only in some cases. The two patients whom I had the opportunity to treat did not respond to irradiation. Dr. Caro recently reported good results with cryotherapy before this society, and I should like to suggest this method for the presented case. It also would be interesting to see what local injections of hydrocortisone (Hydrocortone) acetate might do to these granulomas.

Lichen Striatus? Nevus Unius Lateralis? Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. STEFAN BIELINSKI.

Scleredema(?) of 19 Months' Duration Unresponsive to Corticotropin (ACTH) Therapy. Presented by DR. THEODORE CORNBLEET, DR. DAVID COHEN, and (by invitation) DR. J. F. SICKLEY.

Case for Diagnosis: Dermatitis Repens? Presented by DR. JAMES WEBSTER, DR SAMUEL BLUEFARB, and (by invitation) DR. STEFAN BIELINSKI.

Granuloma Inguinale. Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. J. F. SICKLEY.

Granuloma Inguinale? Presented by DR. HERBERT RATTNER, DR. HAROLD RODIN, and (by invitation) DR. STEFAN BIELINSKI.

Pityriasis Lichenoides et Varioliformis Acuta (Habermann's Disease). Presented by DR. MICHAEL EBERT, DR. ALLEN PEARL, and (by invitation) DR. J. F. SICKLEY.

Papillary Nevus. Presented by DR. DAVID OMENS and (by invitation) DR. HAROLD OMENS and DR. J. F. SICKLEY.

Familial Benign Chronic Pemphigus. Presented by DR. PAUL R. GRIFFITH.

Pseudopelade. Presented by DR. A. W. STILLIANS.

Dermatitis Vegetans of 10 Years' Duration. Presented by DR. A. W. STILLIANS.

Onychatrophia. Presented (by invitation) by DR. JAMES K. TOMPKINS.

Diphenylhydantoin (Dilantin) Sodium Eruption. Presented by DR. JULIUS GINSBERG and (by invitation) DR. BERNARD J. PASS.

Parakeratosis Variegata. Presented by DR. HAROLD SHELLOW.

Congenital Ectodermal Dysplasia (Hair and Nail Changes). Presented by DR. ALBERT H. SLEPYAN.

Poikiloderma Atrophicans Vasculare (Jacobi). Presented by DR. OLIVER RIAN, Peoria, Ill.

Hydroa Vacciniforme. Presented by DR. ALFRED B. FALK and (by invitation) DR. FRANCIS HETREED.

Poikiloderma of Civatte? Presented by DR. IRENE NEUHAUSER.

MANHATTAN DERMATOLOGICAL SOCIETY

Jack Wolf, M.D., President

George M. Lewis, M.D., Secretary

Oct. 14, 1952

Leprosy (Lepromatous Type) Improved by Isoniazid (Nydrazid; Isonicotinic Acid Hydrazid). Presented by DR. MAURICE J. COSTELLO.

R. R., a Puerto Rican woman aged 25, was seen by Dr. Walter Gassner complaining that she burned her hands and forearms frequently. Examination at that time revealed third-degree burns of the hands and forearms, a nodular eruption of the extremities, loss of the outer third of the eyebrows, enlargement of the lobes of the ear, anesthesia, rhinorrhea, crusts in the nasal vestibule, hyperpigmented and hypopigmented areas on the body, interosseous atrophy, retraction of the fourth and fifth fingers of the right hand, flattening of the thenar and hypothenar eminences, enlargement of the ulnar and greater auricular nerves, and ulcerations of the tips of the fingers. Leprosy bacilli were found on the skin in 8 of the 15 locations in which they were sought.

Treatment has consisted of 100 mg. of isoniazid (Nydrazid; isonicotinic acid hydrazid) four times a day for the past two months. There has been definite improvement.

Three children of this patient, all of whom were born in Puerto Rico, have been examined. One of them presents an eruption on the legs.

DISCUSSION

DR. FRANK C. COMBES: This is a lepromatous type of leprosy. Dr. Costello gave a large dose of isoniazid; about 6 mg. per kilogram is the largest dose I have ever given. I am not convinced that isoniazid is better than the sulfones in the treatment of leprosy. Dr. Costello has said that the erythema-nodosum-like lesions have disappeared. I wonder if the patient has not been given one of the sulfones, which we know are very prone to produce these erythema-nodosum-like lesions which persist for many months and which disappear spontaneously. We know that isoniazid is not prone to cause them. My own experience has been rather limited, as we have given the drug to not more than 10 patients, but I have not been impressed with any improvement resulting from the use of isoniazid. At present I am conducting a series of scrapings to evaluate the bacteriologic findings after several months' treatment with isoniazid in comparison to what they were before. These studies have been done with only two patients, and the status of the disease was almost the same as before treatment. I was able to find acid-fast bacilli, and I have not found nonacid-fast rods or globoid forms, as I had hoped. There were approximately the same number of acid-fast rods as before treatment. That has been the experience of those at Carville.

DR. NATHAN SOBEL: I was interested in what Dr. Combes said about the lack of disappearance of the organisms during therapy. That has always applied in the nodular form of leprosy with the sulfones too. Whenever sulfone therapy has been beneficial it has taken years of treatment before the organisms disappear from the skin. There may have been too short a period of observation in this case to enable evaluation of the result.

DR. MAURICE J. COSTELLO: I presented this patient as having been definitely improved by isoniazid (Nydrazid; isonicotinic acid hydrazid) because I thought that it was in line with the experience we have had with other cases at Bellevue. I was under the impression that there was improvement in some of those cases of the lepromatous type. This patient received no sulfone drugs. The first drug she ever received was isoniazid. The lesions have improved, her appetite is better, and she has gained weight. Whether that was due to the isoniazid therapy I do not know, but certainly the improvement paralleled the administration of the drug.

Tinea Capitis (Trichophyton Cerebriforme). Presented by DR. ANTHONY C. CIPOLLARO.

D. N., a woman aged *22*, noted about 11 years ago an area of scaliness and loss of hair on the back of her head, which subsequently spread to other areas of the scalp. She also has noted occasional round scaly lesions on her hands and arms. Through the years she has applied various medicaments, with no improvement. In Caracas, Venezuela, the organism cultured was said to be Trichophyton epilans.

On the crown there is a diffuse alopecia characterized by short curled-up hair which are broken off at the surface and are imbedded in the corium, appearing as black dots. There is a mild perifollicular inflammation, with some scales over the follicular orifices. The epidermis is also moderately and diffusely scarred in the areas of alopecia. On the arms are seen a few dime-sized areas of erythema and slight scaliness.

Potassium hydroxide mounts of the short hairs revealed an endothrix infection. Culture from the hairs on Sabouraud's medium at room temperature produced a moderately slow-growing colony. The periphery was yellowish-white and granular, around a slightly darker heaped-up center. The substrate was reddish-brown and extended beyond the margins of the surface growth. Potassium hydroxide mounts from the culture revealed many branched hyphae with intercalary lateral and larger terminal chlamydospores. Microconidia were present *en thyrse*. No macroconidia were noted. The organism was identified as being in the crateriform series, probably Trichophyton cerebriforme (T. epilans).

The patient is presented for therapeutic suggestions.

DISCUSSION

Dr. George M. Lewis: This is a very interesting presentation, and there are many points to bring out. First, the patient is out of the age range that we usually associate with tinea capitis. However, as Pipkin and others have found, eruptions due to this organism are not confined by any means to children. A skin condition such as this may be easily overlooked and misdiagnosed, since the lesions present today are not those usually seen in tinea capitis. Notable is the atrophy and the small crusted lesions which, if removed, will undoubtedly contain stubs of hairs. If one depends upon Wood's light for verification the infection may be missed, since fluorescence is rarely observed. In this case there is minimal inflammatory reaction, but in other cases considerable reaction may develop, even up the development of kerion capitis. The prognosis is variable, depending on the degree of tissue reaction. Some of our cases have proved completely rebellious to all types of therapy. I would certainly favor x-ray epilation in this case and believe that it is the best hope of cure, even admitting that there may be a recurrence after epilation. The difficulty of not being able to follow the case with Wood's light makes careful attention to manual epilation imperative. A statement should be obtained from the patient or his family that atrophy is present now, and that it is agreed that when the hair regrows after x-ray epilation the result will not be perfect.

Dr. Paul Gross: Does this fungus ever affect the fingernails?

Dr. George M. Lewis: Yes, but rarely.

Dr. Jack Wolf: I would be in favor of x-ray therapy. One must differentiate between the atrophy the patient now has from the disease and that resulting from x-ray therapy, which I think involves no danger.

Dr. Isadore Rosen: In looking at the scalp one gets the impression that the patient is suffering from the end-result of an old favus infection; the dissemination of the atrophy with its associated alopecia is unusual in a tinea infection. I would hesitate to use x-rays unless other methods have been unsuccessful.

Dr. Samuel M. Peck: I was interested in what Dr. Lewis said—that some patients respond easily and others do not. Here we have a fungus in which a positive reaction to the trichophytin test shows a negative result will respond much less easily to local therapy. What interested me particularly were the superficial scaling lesions on the trunk and arms, exactly the same type of lesions as those seen in girls approximately this age or younger, with no evidence of fungous infection. I think that the lesions are due to a Streptococcus infection. They certainly do not show fungi, and one certainly would not think of looking for ringworm of the scalp. I should like to ask the presenter whether the trichophytin test was done, and, if it is possible, I would try local means of therapy. Personally, because of the atrophic lesions already present, I would hesitate to use x-rays.

Dr. Paul Bechet: Clinically, the scarring bears a close resemblance to that observed in a mild case of folliculitis decalvans. The microscopic evidence, however, definitely confirms the correctness of Dr. Cipollaro's diagnosis.

Dr. Frank C. Combes: I am interested in the public-health aspect of this case. How long has this woman had the fungi in her scalp, and is there evidence that she has infected contacts? She certainly must have infected somebody if she has had it for long. Does she go to hair-dressers, etc.?

Dr. Paul Gross: I agree with Dr. Rosen that the condition resembles favus, including the skin lesions which are seen in the herpetic type of favus. Judging from experience with favus, I would not hesitate to use x-ray therapy in this case despite the presence of atrophy. The precautions outlined by Dr. Lewis should be taken.

Dr. George M. Lewis: I might mention a point about the name of the organism. Most mycologists now classify the fungus as Trichophyton tonsurans.

Dr. Anthony C. Cipollaro: I believe that these cases are more common than we think, perhaps because there is no fluorescence under Wood's light. We have two other patients with this condition in the clinic, children in one family who have been treated for a long time with various topical remedies. I think that we will find more if we search minutely with cultural studies.

The trichophytin test was not done in this case. No other members of the family have the disease; so far as we know the patient has not transmitted it to others. She knows that she has something contagious and avoids contacts, so for that reason alone we have to do something more than give topical remedies for another 11 years. I think that x-ray epilation will be effective. We have seen tinea capitis even from Microcsporum audouini, which produces atrophy and scars, so I am not greatly concerned about that.

Lupus Vulgaris Responsive to Isoniazid (Rimifon; Isonicotinic Acid Hydrazid). Presented by DR. NATHAN SOBEL.

R. S., a woman aged 48, was first seen at the skin and cancer unit, New York University Hospital, on Oct. 22, 1951. A band-like scarred area about 4 in. (10 cm.) wide extended from behind the left ear along and beneath the left jaw to several inches to the right of the midline. There were many "apple-jelly" nodules in the periphery of the affected area; the portion behind the ear consisted of a solid plaque.

The patient was born in the United States, lived in Italy from 1915 to 1924, and then returned to the United States. About 1916 a cold abscess developed beneath the chin, which eventually healed, with deep scar formation. About 1943 there was rapid spread of the lesion to its present extent. A roentgenogram of the lungs in 1947 showed a normal picture. Since 1947 she was given many Kromayer light treatments and calciferol at various times.

Examination of the nasal mucosa on Sept. 26, 1952, showed no nodules present. A hemogram and urinalysis gave normal results, and serologic reactions for syphilis were negative. Biopsy done on Oct. 24, 1951, revealed lupus vulgaris.

There was little improvement with injections of streptomycin, 1 gm. three times a week, given from November, 1951, to March, 1952. From June 2 to Aug. 18, 1952, she took 50 mg. of isoniazid (Rimifon; isonicotinic acid hydrazid) three times a day. The nodules have almost completely cleared up.

DISCUSSION

DR. PAUL GROSS: This is an excellent therapeutic result. Comparing the simplicity of treatment and prompt response with the slow and tedious therapy of lupus vulgaris with Finsen light, one must admit the great advance of chemotherapy, even in tuberculosis. I would suggest removing the residual nodules individually by electrocoagulation if they prove resistant to further chemotherapy. Incidentally, this is another case of lupus vulgaris in which there was development around a sinus from a tuberculous lymphoma.

DR. MAURICE J. COSTELLO: The point Dr. Gross just made is interesting and not too well known, i. e., that in a person with tuberculous adenitis lupus vulgaris overlying the tuberculous focus rather than scrofuloderma may develop, and that it usually persists for years. I have seen it frequently enough.

DR. FRANK C. COMBES: There is no doubt that isoniazid therapy is the best treatment we have ever had for lupus vulgaris. Everyone here has had a rather limited experience, as I have. I have noted a temporary flare-up in these lesions after beginning treatment, like the Jarisch-Herxheimer reaction, and I wondered whether others have noticed it before improvement is evident?

DR. DAVID BLOOM: I have seen this patient from time to time during the past few years. Previous treatment with calciferol and dihydrostreptomycin resulted in unsatisfactory improvement. After administration of isoniazid the patient showed great improvement.

DR. NATHAN SOBEL: I agree with those who say that after tuberculous sinuses cases of lupus vulgaris are seen. We have seen them too. Concerning the ultimate effect of isoniazid (Nydrazid; isonicotinic acid hydrazid) we shall have to follow these patients. There are many cases in which the tubercle bacilli develop resistance. The administration of the drug was stopped in this case in the middle of August. We shall probably continue to use it and see if it is necessary to employ other, destructive measures.

Multiple Keloids Occurring in Four Generations. Presented by DR. DAVID BLOOM.

Telangiectasia Macularis Eruptiva Perstans with Lesions in Bones. (A Variety of Urticaria Pigmentosa.) Presented by DR. ORLANDO CANIZARES.

MINNESOTA DERMATOLOGIC SOCIETY

Elmer T. Ceder, M.D., *President*
Harold G. Ravits, M.D., *Secretary*
Nov. 21, 1952

Erythema Induratum? Tuberculous Ulcer? Presented by DR. FRANCIS W. LYNCH, St. Paul.

Mrs. R. E. L., aged 60, first presented an inflammatory plaque on the lower portion of the right leg in 1945. It was about 1 in. (2.5 cm.) in diameter and showed central softening. Twenty months previously she had a severe respiratory infection, followed by development of pulmonary tuberculosis, treated by rest in bed for three months. Since that date there has been periodic observation of the chest, but no evidence of reactivation of the tuberculous process has been found.

In October, 1951, an ulcer appeared anteriorly on the right leg at the site of some insect bites. This failed to respond to antibiotic applications, rest, and the use of Panthoderm (a water-miscible cream containing 2% Panthenol [the alcoholic analog of pantothenic acid]). On Nov. 11, 1952, the ulcer measured 17 by 38 mm. in diameter. Treatment with isoniazid was begun on that date in a dose of 100 mg. twice daily.

DISCUSSION

DR. GILJE, Oslo, Norway: I should like to hear what impression you have of the combined treatment of isoniazid and elastic bandage. I know you use it, and I should like to know if anyone has had experience with it. In erythema induratum we find that the lesions heal much more quickly when we use adhesive tape and elastic bandage.

DR. JOHN KRAFCHUK, Minneapolis: We have had the opportunity at the university hospitals to study several cases of cutaneous tuberculosis in which there was treatment with isoniazid over the past six months. In a 40-year-old white woman with severe erythema induratum of six years' duration dramatic and complete clearing of all lesions took place in three to four weeks, and now, four months later, she is still free of any gross or microscopic activity in the affected areas. In two cases of lupus vulgaris definite improvement has been shown, but not complete clearing with this form of therapy. Of two cases of primary inoculation tuberculosis of the skin in one, the case of a 17-year-old boy, clearance occurred after streptomycin and paraaminosalicylic acid therapy. In the other, the case of a 40-year-old white woman, in which there was no improvement with a similar regimen, the lesions have cleared with isoniazid therapy.

DR. H. E. MICHELSON, Minneapolis: I think that Dr. Gilje wanted us to discuss our general attitude toward the treatment of lower-leg ulcers. I have talked about this before our group many times, and I have been open in my criticism of the treatment most patients receive, that is, almost immediate operation without the previous conservative treatment. The mere presence of enlarged veins does not call for an operation. It is a matter of how competent the circulation is. An ulcer, too, is no indication for operation. One must realize that the time limit is so important, and it is hard to understand why patients wait until these conditioins become so severe before asking advice. It has to do with the social and intellectual classification of the patient. Leg ulcers also are of great economic importance. An equation has been devised in which the size of the ulcer divided by the duration of its presence gives an index to the length of time it will take for healing. On our service at the university we see a rather large number of patients whose legs have been ligated and who have been given injections and who still have a great deal of trouble. This usually occurs one, two, or three years after these procedures. We then put the patient to bed with conservative treatment such as compresses, pressure bandages, strapping, and Unna casts, and very often the result is very pleasing. We stress to the patient the great need for returning at the slightest sign of an ulcer. If we accept the

diagnosis of erythema induratum in this patient we assume it is tuberculosis. If the lesion ulcerates it could be called ulcerated erythema induratum. A tuberculous ulcer, on the other hand, occurring on the leg is not the same as a tuberculous ulcer on the mucous membrane.

Hyperpigmentation, Hypopigmentation, and Pigmented Patches on Lips and Soft Palate in a Patient with Addison's Disease. Presented by ANCKER HOSPITAL STAFF.

Condyloma Acuminatum or Verruca Vulgaris. Presented by DR. JOHN F. MADDEN, St. Paul.

Granuloma of the Palate From Dentures. Presented by DR. FRANCIS W. LYNCH, St. Paul.

Pigmented Spots of the Lips and Buccal Mucosa Associated with Generalized Intestinal Polyposis—Peutz Syndrome. Presented by ANCKER HOSPITAL STAFF.

NEW YORK DERMATOLOGICAL SOCIETY

George C. Andrews, M.D., *President*

Maurice J. Costello, M.D., *Secretary*

Oct. 28, 1952

Generalized Steatoma Associated with Hypercholesteremia. Presented by DR. GEORGE M. LEWIS.

D. E., an Italian woman, aged 33, is presented from New York Hospital with an eruption on the scalp, postauricular areas, face, forearms, chest, buttocks, and vulva, of about 20 years' duration. When the patient was first seen on April 8, 1952, she gave a history of nodules having developed on the skin starting at about the age of 11. They have been appearing in increasing numbers over the past 20 years, being most numerous on the scalp, behind the ears, forearms, neck, and vulva, but excluding almost no part of the integument. They have shown no tendency to undergo involution and have been entirely asymptomatic.

There is a history of nodules on the skin which goes back six generations on the paternal side. One sister and a paternal aunt have diabetes. The patient's youngest child (8 months old) has had milia and comedones almost since birth.

In 1948 it was noted that the patient had bilateral hilar lymphadenopathy and splenomegaly extending to two fingerbreadths below the costal margin. The hilar enlargement regressed in 1950, but recurred early in 1952. A presumptive diagnosis of lymphoma was made, but has never been proved. Biopsies of a lymph node taken on two occasions showed a nondiagnostic picture .

The total cholesterol concentration was 372 mg. per 100 cc. and cholesterol esters 226 mg. per 100 cc. (60.8%).

Biopsy of a nodule from the left forearms showed the epidermis to be uninvolved. There were two large cysts in the cutis, one filled with sebaceous gland elements. The cyst wall was full-thickness epidermal cells. Some amorphous debris was also present. A diagnosis of sebaceous cyst was made.

DISCUSSION

DR. MAURICE J. COSTELLO: It is a little different from my idea. Some of the lesions were flat and solid, suggesting xanthelasma. The one having an irregular shape might be investigated.

DR. JOHN H. MEYERS (by invitation): We were interested in the possibility that the lesions were xanthomatous in character. I did pick out one of the type which Dr. Costello described for examination, and that proved also to contain only sebaceous material. It was because of the initial impression of xanthoma that the cholesterol values were obtained.

DR. WILBERT SACHS: I wonder if there is any objection to calling it steatoma multiplex congenitale. Very few cases have been described in the literature under the term, and without the "congenitale" there are many. These lesions are to a great extent characteristic of those in a case I published many years ago. Unfortunately, at that time we did not look for cholesteremia.

DR. JEAN CRAMER (by invitation): It is of interest that the patient's lipoprotein level is abnormal, showing a shift from the normal proportion between the alpha- and beta-fractions,

somewhat similar to that seen in familial hypercholesteremia. It is not as severe, but demonstrates a like abnormality. It was because of the initial impression of xanthoma that the lipoprotein determinations were made.

DR. GEORGE C. ANDREWS: I also think that it is very unusual, especially the association of infantile acne with steatomatosis. I have seen it in a family involving several generations, but I have never seen a baby so affected.

DR. FRANK C. COMBES: I wonder whether it is a real acne? If a lesion were taken out would it show a follicular parakeratosis or would it show merely inspissated sebum?

DR. GEORGE C. ANDREWS: I think that the infant shown tonight had definite acne, with comedones, papules, pustules, and little cysts.

DR. FRANK C. COMBES: I was interested in the question of parakeratosis.

DR. GEORGE C. ANDREWS: In not all cases of steatomatosis is there hypercholesteremia. Many patients have normal values, so Dr. Sachs's and Dr. Cramer's suggestion that this is a congenital type of hypercholesteremia is important, and it must be differentiated from ordinary steatomatosis.

DR. GEORGE M. LEWIS: It is gratifying to know that some of the members see the resemblance to xanthomatosis, because that was our first impression. The specimen for biopsy was taken from a lesion that was more suggestive of xanthoma than some of the lesions we have seen tonight.

Tinea Capitis (Trichophyton Cerebriform or Crateriform). Presented by DR. ANTHONY C. CIPOLLARO.

D. N., a woman aged *22*, was previously presented before the Manhattan Dermatological Society on Oct. 14, 1952, complaining of scaliness and loss of hair of 11 years' duration. She has also noted occasional round scaly lesions on her hands and arms. The causative organism was identified as being in the crateriform series, probably Trichophyton cerebriforme.

DISCUSSION

DR. GEORGE M. LEWIS: X-ray therapy is not a certain cure for this type of ringworm of the scalp. It is perhaps the best single treatment we have, but the after-treatment is extremely important, more so than in cases of Microsporum audouini infection. These patients should be followed very carefully for several weeks, as reinfection or latent infection is commonly encountered. As was brought out in the presentation, these three cases illustrate the variability of clinical manifestations. Infection is apt to start insidiously and to be overlooked or misdiagnosed. Important is the lack of fluorescence of these hairs under Wood's light. That being the case, the alert dermatologist must take scrapings or cultures. It is apparent that such cases may remain undiagnosed for many months. We have a series of patients we have observed over the past few years. I am not sure there is an actual increase in the incidence of the disorder; because of the recent publicity, it may be diagnosed more often. It is prevalent in Mexico and is also seen in Texas and California. The patients shown tonight were from Malta and Venezuela.

Lupus Vulgaris Treated with Isonicotinic Acid Hydrazid (Rimifon). Presented by DR. EUGENE F. TRAUB.

F. J. A., a woman aged 57, had lupus vulgaris at the age of *2* on the left cheek. It has remained confined to that general area, growing slowly until a few years ago when a more rapid growth occurred after the death of her husband. One area just anterior to the left ear showed exudation or ulceration. The question of malignant change was considered. The patient was given Rimifon (isonicotinic acid hydrazid) in 50-mg. doses, because it was more easily obtainable than Nydrazid (isonicotinic acid hydrazid).

The blood cell count was normal on Sept. 24, 1952, and urinalysis showed no albumin or sugar, with a few leucocytes and red blood cells.

Lupus Vulgaris Treated with Iosiniazid (Nydrazid; Isonicotinic Acid Hydrazid). Presented by Dr. George M. Lewis.

S. L., a man aged 66, is presented from New York Hospital with a history of having had lupus vulgaris for 50 years. Recently urinary symptoms developed which was found to be due to carcinoma of the right kidney which was removed and to benign prostatic hypertrophy. Lupus vulgaris has been present on the right heel for 50 years and has been never treated. Lesions had also developed and been treated on the left angle of the mouth 38 years ago, on the forehead 34 years ago, and on the left side of the chest 28 years ago.

On examination there was a brownish-red infiltrated erythematosquamous plaque on the posterior aspect of the right heel, extending to the inner aspect of the ankle. "Apple jelly" nodules were present.

Roentgenograms of the chest showed a normal picture. The tuberculin test gave a positive reaction in a dilution of 1 : 1,000,000.

Biopsy showed that the cutis, below an overlying acanthosis and hyperkeratosis, contained a solid mass of chronic inflammatory tissue with numerous plasma cells, clusters of epithelioid cells around central giant cells, and one central area of caseation necrosis.

Treatment has consisted of iosiniazid (Nydrazid; isonicotinic acid hydrazid) 100 mg. twice daily for three months. To date the lesions have undergone involution some 75%.

Lupus Vulgaris Treated with Iosiniazid (Nydrazid; Isonicotinic Acid Hydrazid). Presented by Dr. Eugene F. Traub.

J. S., a farmer aged 42, had lupus vulgaris at the age of 6, and it has been progressive since that time. Because of the extensive involvement of his face, innumerable plastic removals and repairs have been performed. He has had various types of treatment including desiccation, cauterization, and administration of calciferol internally. At no time has the disease been arrested.

Iosiniazid (Nydrazid; isonicotinic acid hydrazid) therapy was begun on June 2, 1952, and six weeks later all activity except for a few tiny areas had apparently disappeared. Two months later no sign of active lesions could be found.

DISCUSSION

Dr. Leslie P. Barker: While lupus vulgaris responds favorably to treatment with isonicotinic acid, the tuberculids do not. I have treated several patients with erythema induratum and papulonecrotic tuberculid with this drug, and they have shown no improvement.

Dr. Frank E. Cormia: I agree with Dr. Barker regarding the tuberculids. I have followed two patients with lupus vulgaris, and they have both responded to a daily dose of 200 mg. of isonicotinic acid hydrazid. This dose is relatively small compared with that given for active systemic tuberculosis. If the tuberculid group of patients have an active focus of tuberculosis, isonicotinic acid hydrazid should affect that focus. It may be that the organisms are relatively resistant. It has been shown that the tubercle bacillus may acquire resistance to isonicotinic acid hydrazid, although the phenomenon is not apt to be permanent. Grace and his associates have stated that isonicotinic acid hydrazid should never be given alone, but should be combined with streptomycin, paraaminosalicylic acid, etc.

Dr. Maurice J. Costello: We must be careful in making any statement that isonicotinic acid hydrazid (Nydrazid) is not effective in treating erythema induratum when we are talking about only half a dozen cases among all of us. I have one in which it was quite effective. To my knowledge, it is the best treatment for true cutaneous tuberculosis.

Tinea Capitis with Kerion (Trichophyton Crateriforme). Presented by Dr. George M. Lewis.

Case for Diagnosis: Pigmentary Disturbance of the Lower Extremities. Presented by Dr. Anthony C. Cipollaro.

Calcinosis Cutis Occurring After a Burn. Presented by Dr. George M. Lewis.

Bowen's Disease (Single Lesion) of the Finger. Presented by Dr. Maurice J. Costello.

George C. Andrews, M.D., *President*

Maurice J. Costello, M.D., *Secretary*

Nov. 25, 1952

Case for Diagnosis: Pyoderma? Onychomycosis? Psoriasis? Presented by Dr. Leslie P. Barker.

R. M., a man aged 56, had a persistent infection around the base of both little fingernails which began in March, 1950. He consulted a dermatologist, who also found some thickening of the left heel and who made a diagnosis of psoriasis. There was no improvement after three x-ray treatments, and the patient consulted another dermatologist, who said that he had infected nails and gave him penicillin injections for several days and who then advised hospitalization when no improvement ensued. During his 10-day period of hospitalization he received large doses of penicilin and hot soaks. Intravenous aureomycin was also given, but was discontinued after the second injection because of a febrile reaction. During this time the condition of the little fingernails improved, but other fingernails became infected, with the condition always beginning as a paronychia and involving the nails secondarily.

In June, 1950, he consulted a surgeon, who removed the little fingernails, and from then on until May, 1952, four fingernails on the left hand and two on the right were removed several times, and, finally, the matrix was destroyed on three nails. Pus has continued to form in pinpoint-sized pockets in the nail bed and around and beneath several remaining nails.

Repeated cultures of the nails and tissue taken at operation always showed Staphylococcus albus. Many antibiotics were used internally, including oxytetracycline (Terramycin), chloramphenicol (Chloromycetin), and the sulfonamide drugs.

The left third and fourth fingernails are replaced by scar tissue, and several pinpoint drops of pus can be expressed from the nail bed on pressure. Other nails are distorted from operation, and pus can be expressed from the edges of several of these. Both thumbnails show some pitting suggestive of psoriasis, and the right thumbnail has several small islands of brownish discoloration beneath the nail plate, which contain whitish pus when the nail is cut back. The right little fingernail is thickened, pithy, and has several small pus pockets under the distal third.

Roentgenograms of the left hand show no bone or joint involvement.

Examination of the paranasal sinuses revealed normal findings. The tonsils are enlarged and show chronic infection, and the patient has been advised by an otolaryngologist to have them removed. X-ray examination of the teeth revealed one abscess, and the tooth was removed two weeks ago.

Intradermal tests gave a negative reaction to Candida albicans in a 1:500 dilution and to Trichophyton in a 1:100 dilution and a 3+ reaction to Staphylococcus toxoid.

Repeated cultures from infected nails and pus beneath the nails taken since October, 1952, grew Staphylococcus aureus, but no fungi.

Reports at the time of the various operations always showed normal findings for the erythrocyte sedimentation rate, the serologic examinations, and the blood counts, with the exception of an elevated white blood cell count of 12,600, with a normal differential count, on two occasions.

DISCUSSION

Dr. George M. Lewis: I see no evidence of fungous infection and would also hesitate to make a diagnosis of psoriasis on the present findings. I question the advisability of any radical therapy at this time. The patient has some permanently avulsed nails. He may be in the class of a habitual picker or traumatizer and should be discouraged from further destructive therapy.

Dr. Gerald F. Machacek: This picture is confused by the man's personality. There are iatrogenic factors in the case. The probability is that he had psoriasis which was treated much too strenuously. Otherwise, I must agree completely with Dr. Lewis.

Dr. Carl T. Nelson: I rather think that if on repeated culture one has found staphylococci but no fungi, one has to assume that this man has a staphylococcic paronychia, recurrent and severe. It may be a factitial process, induced by persistent trauma, such as picking.

DR. ANTHONY C. CIPOLLARO: I agree with the three previous speakers. This man does have some nail changes; if you look at his thumbnails closely you will find changes possibly suggestive of psoriasis—brownish discoloration, involvement of only a portion of the nails, with the process leading approximately to the paronychial tissues. I think that he might have overtreated psoriasis. The neurological status of this person makes one think that he may be traumatizing the lesions.

DR. MAURICE J. COSTELLO: I agree that the lackluster appearance and the pitting would suggest psoriasis of the nails. The patient was probably told that he had a fungous infection. He probably has a fixation, and I think that picking may be largely responsible for his present condition. He needs the services of a psychiatrist.

DR. FRANK E. CORMIA: There may be a factitial element in this case, as has been pointed out, but I doubt whether the patient could be persuaded to go to a psychiatrist and I do not think that would be either feasible or successful. Possibly the infectious element is a Staphylococcus which is resitant to the antibiotics used. Perhaps one could be found which would prevent further relapses of the pyogenic complication.

DR. J. LOWRY MILLER: I would favor a basic diagnosis of psoriasis, with overtreatment and secondary infection as subsequent factors.

DR. FRANK C. COMBES: I did not see the patient, but in regard to pitting of the nails, if one looks closely, the depths of the pits are lusterless in fungous infections, whereas in psoriasis they are shiny. If the affection is confined to the nail plate I do not think that we are justified in making a diagnosis of psoriasis. Psoriasis is a dermatologic disease. We see changes in the nails, identical as far as pitting is concerned, in lichen planus, in involutional diseases, and in disturbances in lipid metabolism. I do not think that pitting of the nails of itself should justify a diagnosis of psoriasis in any instance, no matter how typical it may appear.

DR. GEORGE C. ANDREWS: I have been impressed for years by the frequency of recurrent boils limited to the tips of the fingers of pianists. This man types a great deal, and there is possibly a traumatic effect. Also, there is a question of these nail changes being due to peripheral vascular disease. He is 56, and the condition started at 54. The strange thing is that he has had these 150 boils or operations and nobody has tried a vaccine. Dr. Cormia's suggestion that this may be due to a Staphylococcus that is resistant to all the antibiotics used against it and that might respond to someting else, such as vaccine therapy, is worth considering.

DR. EUGENE F. TRAUB: The man did have some arthritis, and I am wondering whether there is any connection there with the nail condition. Finding a Staphylococcus would not rule out psoriasis.

DR. MAURICE J. COSTELLO: The Staphylococcus is the organism found in infections of the skin of this type. One may find arthritis of the distal joints, with thickening of the distal phalanx, laterally and anteroposterioly, and psoriasis confined to the nails.

DR. LESLIE P. BARKER: This patient is undoubtedly very nervous. He picks and squeezes his fingers, trying to obtain pus. This may account for the recurring pyoderma in the old nail beds, but I do not believe that it could be the cause of his original nail disease. Brownish islands of discoloration develop in the nails that contain pus beneath the nail plate. He also has some pitting of several nails, which I think is very indicative of psoriasis.

Nevocarcinoma. Presented by DR. ANTHONY C. CIPOLLARO.

L. G., a woman aged 20, first consulted me on Nov. 22. She had had a mole on the anterior surface of the left thigh since birth, which was brownish and which showed no change for the first 15 years. About five years ago, however, it began to spread peripherally, becoming elevated during the past year. During the past several months the lesion has exuded a blackish fluid. She had never consulted a physician about the lesion until a few days ago.

The patient appears to be a well-developed well-nourished, healthy young woman. There is a lesion on the anterior surface of the midportion of the left thigh, circular in shape, with a diameter of about 3 cm. It is elevated and sharply demarcated from the normal surrounding skin, but does not appear to be deeply infiltrated. The highest point of elevation is about 3 mm.,

and the color is brownish, almost black. It is exuding a dark-brownish fluid, no doubt due to slight trauma. The patient does not protect the area because she says that a bandage sticks to it. There are no areas of pigmentation in the surrounding skin and no similar lesions elsewhere on the body. The inguinal lymph nodes are not palpable. There are no symptoms referable to other organs.

DISCUSSION

DR. LESLIE P. BARKER: I think that this is a malignant melanoma and should be extensively removed.

DR. WILBERT SACHS: I agree with the concept that I am sure most of the members have. However, I should like to see a biopsy performed before treatment is undertaken, because if it turns out to be nevocarcinoma there will have to be an exceedingly wide removal. If it should turn out to be something else it would not require as wide an excision.

DR. FRANK E. CORMIA: The lesion has a very angry, malignant look to me, and while the degree of malignancy may be relatively low, I think that wide excision should be done. A plastic or general surgeon would do a good job. I disagree with Dr. Sachs regarding biopsy; I do not think that it should be performed.

DR. EUGENE F. TRAUB: I think that without a doubt it is nevocarcinoma, in a nevus present since early infancy, and that gives a better prognosis. Since it arose on a preexisting lesion I think that local excision will suffice. I do not see why this lesion could not be removed in the office; it can be excised with the electric cutting current and allowed to granulate in from the base. The patient is not laid up and is spared much difficulty. At the same time, the entire lesion can be sectioned without the danger of performing a biopsy, which I do not like either, unless it is done with the frozen-section method at the same time complete removal is performed.

DR. J. LOWRY MILLER: I agree that this lesion should be removed by wide local excision, and I would oppose radical gland dissection. The latter procedure is almost certain to leave a permanent crippling edema which offsets the slightly higher percentage of cure over the local excision. It is much better to take the chance, perform wide local excision, and leave the patient a normal leg. She will probably get an excellent result because of the reasons mentioned—the five years' duration, the fact that it arose from a nevus, etc.

DR. FRANK C. COMBES: I agree with everything that Dr. Traub and Dr. Miller said. The chances are that in 99 cases out of a 100 that is all that is necessary to get an excellent result. I could not consider that I was through with the patient after that. Every six months or so I would watch the femoral and inguinal nodes, particularly the femoral ones in this case. Sometimes, years afterward, metastases occur in one node, and the lesions will remain in this one node without further spread. I am opposed to any radical dissection of nodes at this time.

DR. GEORGE M. LEWIS: I think that one of the poor prognostic signs in this patient is the surface roughness, which indicates growth and possible metastasis. I agree that a conservative procedure is indicated, conservative wide excision or destruction, as Dr. Traub suggests. The end-results from excision in continuity and other radical surgical techniques do not justify their use.

DR. GERALD F. MACHACEK: I should like to call the lesion melanoblastoma. It is malignant, and I agree with those who believe that the lesion should be excised widely and completely. If it were on the face there would be a question of devastating cosmetic effect, which is not a problem here. It is justifiable to take a biopsy specimen in that location, followed by immediate excision. Patients whose lesions were treated with excision of local lymph nodes have not done any better than those whose lesions were just widely excised. Pigmented lesions have a wider variation in their natural history, even though the microscopic anatomy appears to be similar in them.

DR. PAUL E. BECHET: I agree with the diagnosis, as the lesions presents the classic appearance of this type of malignant growth. In my experience, recurrence or metastasis occurs more frequently after simple excision in the young than in the aged. For that reason I would not rest content with a wide excision alone, but would remove the lymph nodes in the groin as well.

DR. MAURICE J. COSTELLO: It might be well to take an x-ray of the chest. What would be the dimensions of your excision?

DR. ANTHONY C. CIPOLLARO: It is a grave responsibility to handle a case like this, and the physician should be willing to face it. If one is going to be radical one will have to be prepared to consent even to hemipelvectomy. The other extreme is not conservative, but radical in a sense, in that the primary lesion should be completely removed. I have been thinking about this during the last two days and have made up my mind to excise the lesion widely, with approximately ½ or ¾ in. (1.3 or 1.9 cm.) around and underneath the lesion. If the pathologist finds any evidence of malignancy in what appears to be normal tissue around and below it, then this patient already has a type of malignancy that cannot be reached, no matter how radical the surgery. I prefer excision, because the wound will heal more promptly than after electrosurgery.

NOTE.—The lesion was widely and deeply excised on Dec. 5, 1952, and under the magnifying lens there was no evidence of pigmentation in the fat. The histologic diagnosis was early malignant melanoma. The pathologist summarized his findings thus: "Malignant changes have taken place in this highly pigmented dermo-epidermal nevus (junction nevus), even though it is so superficial. No tumor cells were found in the subcutaneous fat."

The wound healed by primary intention.

Case for Diagnosis: Epidermolysis Bullosa Hereditaria? Ichthyosis? Presented by DR. ANTHONY C. CIPOLLARO.

Radiodermatitis of Breast, with Ulceration. Presented by DR. FRANK E. CORMIA.

Obituaries

HARRY PINCUS JACOBSON, M.D.
1888-1953

Dr. Jacobson died at his home in Los Angeles on March 21, 1953, after a long illness. Born in Warsaw, Poland, on July 14, 1888, he came to America while still a child. He was graduated in Medicine from the University of Southern California in 1916 and studied dermatology both here and in Europe. He was a member of the Los Angeles Dermatological Society and of the American Academy of Dermatology and Syphilology. He served as chairman of the Tumor Board of the Los Angeles County General Hospital for 19 years and became Professor Emeritus of Dermatology at the University of Southern California.

Dr. Jacobson will be best remembered for his textbook "Fungous Diseases," which appeared in 1932. Only those who know the previous status of medical mycology can appreciate the monumental effort necessary to extract the essence of truth from a voluminous mass of conflicting literature in such a compact and concise form for the first time in English. He made many contributions to the early study of coccidioidomycosis and was one of the first to utilize coccidioidin as a diagnostic aid. His work on vaccinotherapy in this and other fungous and bacterial diseases was still being pursued at the time of his death. The knowledge of the processes which he developed, together with his laboratory equipment, has been bequeathed to the University of Southern California, where every effort will be made to see it continued.

Obituaries

MARTIN THOMAS VAN STUDDIFORD, M.D.
1891-1953

Dr. Martin Thomas Van Studdiford died in Baptist Hospital in New Orleans on May 15, 1953. There are probably few American dermatologists who have not known this colorful personality, and most of those who knew him would call him Van or Tom and feel that he was their friend.

Born in Jonesburg, Mo., in 1891, he attended Central College at Fayette, Mo., and then went to the University of Missouri, where he graduated with a B.A. degree in 1915. He left home to start his medical studies in St. Louis, but, on an impulse, came to Tulane University in New Orleans. He graduated from Tulane University of Louisiana School of Medicine in 1918 and served his internship at the Presbyterian Hospital in New Orleans. His interest in dermatology became such that he decided to take further training. He studied in St. Louis, New York, and Europe and returned to New Orleans, where he practiced until his death. He became director of all radium and x-ray therapy at the Charity Hospital of Louisiana in New Orleans and later became chief of staff of the dermatology department. He was very much interested in teaching and was, from the beginning of his practice, affiliated with Tulane University of Louisiana School of Medicine. He followed Dr. Ralph Hopkins as Professor of the dermatology department of Tulane University. He was consultant to the National Leprosarium at Carville, La., and with Dr. James K. Howles he was co-founder of the Louisiana Dermatological Society, which has become a great factor in the advancement of dermatological knowledge and training in this area.

Of special interest among his contributions to the dermatological literature were his writings on acne and heavy-metal drug reactions.

His memory will linger with us, who knew him best for his dry sense of humor, his deep interest in people and their problems, and his thoughtfulness in doing things for his friends. Many will remember him in his apartment in the Vieux Carre overlooking Jackson Square and the Cabildo or in his office overlooking the big bend in the Mississippi River.

He was a devout Catholic. May his soul rest in peace.

LEE D. MCLEAN, M.D., New Orleans.

MARTIN THOMAS VAN STUDDIFORD, M.D.
1891-1953

News and Comment

ANNOUNCEMENTS

Italian Society of Dermatology and Syphilography.—The next National Congress of Dermatosyphilology will take place in Rome on Dec. 18, 19, and 20, 1953. The topic for lecture will be "Physiopathology of the Cutaneous Inflammation: Elementary Inflammatory Clinical Statements (Erythema, Pomphus, Blisters, Papula, Node)," with speakers from the schools of Padua, Parma, and Siena. The topic for discussion will be "Present Directions of the Serologic Problems of Syphilis," entrusted to the clinics of Genoa, Modena, and Naples.

Books

Tumors of the Skin: Benign and Malignant. By Joseph Jordan Eller and William Douglas Eller. Second edition. Price, $15. Pp. 697, with 553 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1951.

This is the second edition of "Tumors of the Skin: Benign and Malignant" by J. J. Eller, M.D., and W. D. Eller, M.D. The book contains 697 pages and has 553 illustrations, clinical and histopathologic, most of which are good and demonstrate clearly the point under discussion. More than 100 types of tumors are clinically described, with many microscopic discussions and descriptions of the treatment programs included. Not only irradiation therapy is discussed in detail, but a chapter on plastic surgery in the treatment of skin tumors is also included. There are ample references at the end of each chapter.

The book is recommended to anyone who treats tumors of the skin, whether he be general practitioner, surgeon, dermatologist, or roentgenologist.

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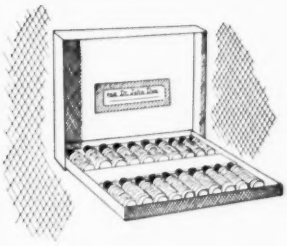

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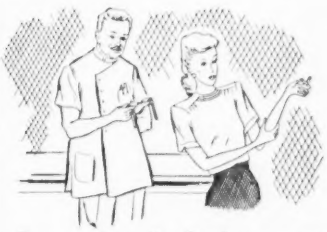

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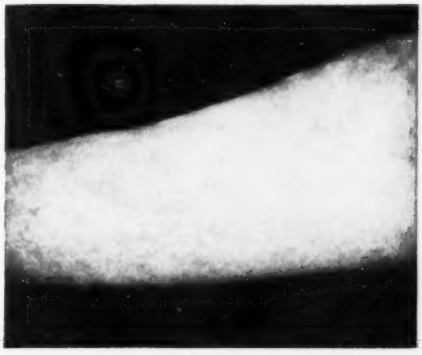

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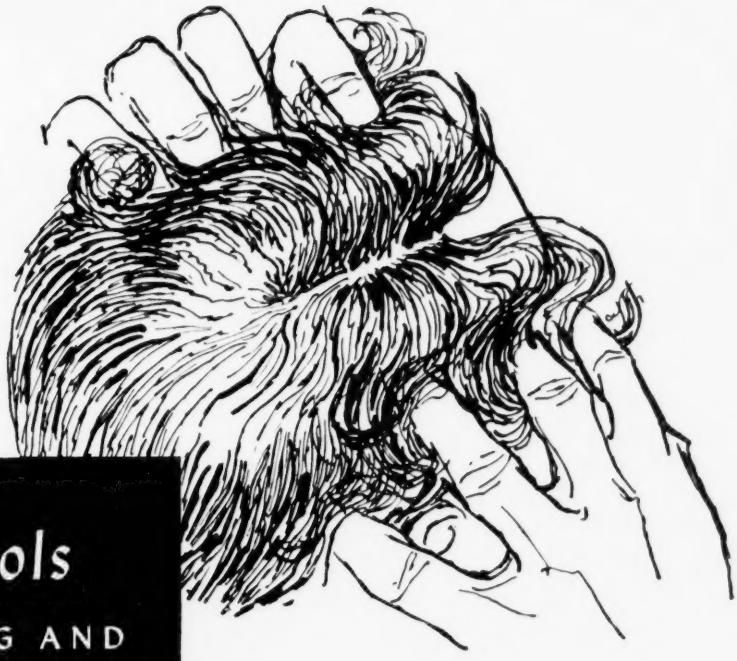

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